

The American Journal of Cardiology

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- | | |
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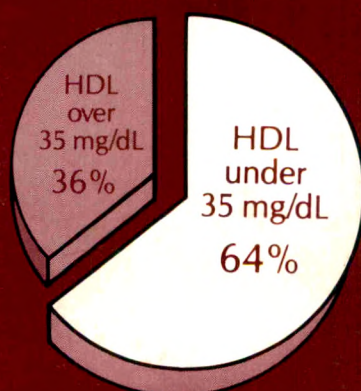
A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

250 TOTAL
35 HDL
mg/dL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,¹ and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.²

HEART ATTACK PATIENTS
(PROCAM TRIAL)²



The American Journal of Cardiology

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A woman with short brown hair, wearing a light purple button-down shirt, is shown from the chest up. She has a look of panic or distress, with wide eyes and a slightly open mouth. She is holding her hands near her chest. The background is a blurred crowd of people, suggesting a crowded public space. A black rectangular box with a red top border is superimposed over the upper right portion of the image, containing white text.

*"I can't breathe...
I have to get out
of here."*

P 24,179

COMING SOON

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TREATMENT OF PANIC DISORDER.

Upjohn

CORONARY ARTERY DISEASE**1281****Usefulness of Late Coronary Thrombolysis (Recombinant Tissue-Type Plasminogen Activator) in Preserving Left Ventricular Function in Acute Myocardial Infarction**

Bruno Villari, Federico Piscione, Domenico Bonaduce, Paolo Golino, Tonino Lanzillo, Mario Condorelli, and Massimo Chiariello

We assessed whether administration of recombinant tissue-type plasminogen activator up to 8 hours after onset of symptoms of acute myocardial infarction may result in a significant improvement in left ventricular function. Data confirm the efficacy of early thrombolysis and suggest that late reperfusion may act beneficially in preserving late ventricular volumes and function.

1287**Usefulness of Antithrombotic Therapy in Resting Angina Pectoris or Non-Q-Wave Myocardial Infarction in Preventing Death and Myocardial Infarction (a Pilot Study from the Antithrombotic Therapy in Acute Coronary Syndromes Study Group)**

Marc Cohen, Philip C. Adams, Linda Hawkins, Matt Bach, and Valentin Fuster

In a prospective 3-month pilot trial of antithrombotic therapy in the acute coronary syndromes of resting and unstable angina pectoris or non-Q-wave myocardial infarction, we randomized 93 consecutive patients to receive aspirin (325 mg/day), or full-dose heparin followed by warfarin, or the combination of aspirin (80 mg/day) plus heparin and then warfarin, while maintaining patients on their standard antianginal medications. Antithrombotic therapy, coupled with early intervention after recurring myocardial ischemia, is associated with a low rate of death or infarction within the first 3 months.

1293**Angiographic Progression to Total Coronary Occlusion in Hyperlipidemic Patients After Acute Myocardial Infarction**

Joe K. Bissett, William L. Ngo, Richard P. Wyeth, John P. Matts, and the POSCH Group

In 413 hyperlipidemic patients with a history of myocardial infarction, we assessed the progression of coronary artery stenosis to total occlusion. This prospective serial angiographic study showed that the extent of initial coronary artery narrowing was significantly associated with the risk of progression to total occlusion.

1298**The Western Washington Myocardial Infarction Registry and Emergency Department Tissue Plasminogen Activator Treatment Trial**

Ralph Althouse, Charles Maynard, Manuel D. Cerqueira, Michele Olsufka, James L. Ritchie, and J. Ward Kennedy

During 1 year, of 1,028 patients with acute myocardial infarction evaluated for eligibility for thrombolytic therapy, 221 (22%) were eligible; 175 (79%) of these 221 were correctly identified by emergency physicians and 160 (72%) were enrolled. The initial management of AMI with recombinant tissue plasminogen activator in the emergency department provided rapid and safe treatment comparable to that reported in trials that started treatment in the coronary care unit.

1304**Ability of Calcium-Entry Blockade by Felodipine to Disclose Different Pathogenetic Mechanisms Behind Hyperventilation-Induced Myocardial Ischemia in Men**

Diego Ardissino, Stefano Savonitto, Paola Zanini, Paolo Barberis, Stefano De Servi, Alberto Rolla, and Giuseppe Specchia

To see if hyperventilation-induced myocardial ischemia occurring during either the overbreathing or recovery stages is based on different pathogenetic mechanisms, we studied 2 consecutive series of patients who developed either early or late ST-segment depression during a run-in hyperventilation test, administering a single oral dose of placebo or of felodipine, a new vasoselective calcium antagonist, on 2 consecutive days in a randomized, double-blind, crossover design. Our findings confirm that early hyperventilation-induced ST-segment depression is related to increased oxygen consumption, which cannot be prevented by felodipine; but, felodipine was highly effective in preventing delayed ischemia, which is due to a primary reduction in coronary blood flow.

1309**Long-Term Prognosis of Myocardial Ischemia Detected by Holter Monitoring in Peripheral Vascular Disease**

Khether E. Raby, Lee Goldman, E. Francis Cook, Joanna Rumerman, Joan Barry, Mark A. Creager, and Andrew P. Selwyn

To assess the long-term prognostic significance of myocardial ischemia, as measured by ambulatory electrocardiographic monitoring, we prospectively studied 176 eligible patients scheduled for elective peripheral arterial vascular surgery. In patients with peripheral vascular disease, who often are unable to perform adequate exercise testing, ambulatory monitoring for myocardial ischemia is a significant independent predictor of long-term prognosis.

1314

Usefulness of Tomographic Thallium-201 Imaging for Detection of Restenosis After Percutaneous Transluminal Coronary Angioplasty

Harvey S. Hecht, Richard E. Shaw, Thomas R. Bruce, Colman Ryan, Simon H. Stertzer, and Richard K. Myler

In 116 patients (61 [53%] with 1-vessel and 55 [47%] with multivessel percutaneous transluminal coronary angioplasty), we evaluated the role of tomographic thallium-201 exercise imaging in the detection of restenosis after PTCA. Single-photon emission computed tomography thallium-201 imaging is an excellent tool for the detection of restenosis and disease progression after 1- or multivessel PTCA and complete or partial revascularization.

1319

Coronary Artery Disease in the Octogenarian: Angiographic Spectrum and Suitability for Revascularization

Glen J. Kowalchuk, Samuel C. Siu, and Stanley M. Lewis

Angiographic findings of 84 consecutive elderly patients with coronary artery disease were examined to determine their suitability for coronary artery bypass grafting and percutaneous transluminal coronary angioplasty. We found that in octogenarians with CAD, cardiac catheterization will often reveal coronary anatomy that is suitable for CABG but less often suitable for PTCA. Morbidity and mortality associated with these interventions are high.

1324

Prevalence and Correlates of Increased Lung/Heart Ratio of Thallium-201 During Dipyridamole Stress Imaging for Suspected Coronary Artery Disease

Flordeliza S. Villanueva, Sanjiv Kaul, William H. Smith, Denny D. Watson, Shailendra K. Varma, and George A. Beller

Multivariate analysis demonstrated that the presence of redistribution and left ventricular cavity dilatation were the most significant correlates of lung/heart thallium-201 ratio in 87 patients undergoing dipyridamole thallium-201 stress testing. Increased pulmonary thallium-201 uptake may be a marker of functionally more significant coronary artery disease.

1329

Sudden Death Behind the Wheel from Natural Disease in Drivers of Four-Wheeled Motorized Vehicles

David H. Antecol and William C. Roberts

We examined the heart and major arteries and reports of other body organs in 30 persons who died from natural disease while behind the wheel of an automobile, truck or bus. The major focus of this report is on the extent of coronary artery disease present and on the frequency and types of myocardial lesions.

SYSTEMIC HYPERTENSION

1336

Changes in Plasma Free Fatty Acids and Glycerols During Prolonged Exercise in Trained and Hypertensive Persons Taking Propranolol and Pindolol

Jacquelyn K. Jesek, Nicholas B. Martin, Craig E. Broeder, Evan L. Thomas, Kathleen C. Wambsgans, Zandrie Hofman, John L. Ivy, and Jack H. Wilmore

The extent to which lipolysis is attenuated at prolonged submaximal exercise during therapy with β blockade was determined in 12 normotensive endurance trained and 12 hypertensive sedentary men using drugs with and without intrinsic sympathomimetic activity. Beta-adrenergic blockade did not attenuate lipolysis in the untrained hypertensive subjects when

compared with results during placebo administration. However, blockade attenuated lipolysis in the trained normotensive subjects when compared with results during placebo therapy.

1342

Effects of Renin Inhibition in Systemic Hypertension

Pamela W. Anderson, Yung S. Do, Morris Schambelan, Richard Horton, Robert S. Boger, Robert R. Luther, and Willa A. Hsueh

The effects of the direct renin inhibitor enalkiren (Abbott Laboratories) on blood pressure, the renin-angiotensin-aldosterone system, and urinary prostacyclin were examined in 8 healthy patients with essential hypertension. Results show that enalkiren is effective in decreasing blood pressure and in inhibiting the renin system, without altering urinary prostacyclin excretion, suggesting that the renin system contributes to the maintenance of elevated blood pressure in some patients with essential hypertension.

CONGESTIVE HEART FAILURE

1348

Importance of Hemodynamic Response to Therapy in Predicting Survival with Ejection Fraction $\leq 20\%$ Secondary to Ischemic or Nonischemic Dilated Cardiomyopathy

Lynne Warner Stevenson, Jan H. Tillisch, Michele Hamilton, Michael Luu, Catherine Chelimsky-Fallick, Jaime Moriguchi, Jon Kobashigawa, and Julie Walden

To identify patients with ejection fractions $\leq 20\%$ who are likely to survive on tailored medical therapy after referral to transplantation, we studied 152 patients before and after vasodilator and diuretic therapy tailored to hemodynamic goals. Although survival with ejection fraction $\leq 20\%$ is better than previously described, early transplantation should be considered when ventricular filling pressure cannot be adequately decreased, particularly if coronary artery disease is present.

VALVULAR HEART DISEASE

1355

Use of Auscultation to Follow Patients with Mitral Systolic Clicks and Murmurs

Oswald B. Tofler and Geoffrey H. Tofler

To determine the clinical significance of an auscultatory classification of mitral systolic clicks with or without precordial systolic murmurs, a cardiologic consultant's medical records of 291 patients with these signs were reviewed. The prognosis for these patients was excellent over an 8-year average follow-up. In particular, patients with apical systolic clicks without murmurs did not develop severe mitral regurgitation or require surgery. Because clinical outcome relates to symptoms and auscultatory findings, an auscultatory classification based on the presence of clicks with or without a murmur may be preferable to an echocardiographic classification for patient management.

MISCELLANEOUS

1359

Quantitative Analysis of Ventricular Late Potentials in Healthy Subjects

Angelo A. Raineri, Marcello Traina, Antonino Rotolo, and Renzo M. R. Lombardo

To define normal value ranges for signal-averaged electrocardiograms, we recorded signal-averaged electrocardiograms in 61 subjects (33 men, 28 women) without evidence of systemic

hypertension or cardiac or metabolic disease. Our results showed a significant difference in QRS duration between men and women, although normalization of QRS duration for height cancelled out that difference, suggesting that adoption of criteria related to either gender or to body characteristics is warranted when interpreting signal-averaged electrocardiographic values.

METHODS

1363

Validation of a Computerized Technique for Detection of the Gas Exchange Anaerobic Threshold in Cardiac Disease

Kenneth Dickstein, Stale Barvik, Torbjorn Aarsland, Steven Snapinn, and Jay Millerhagen

Respiratory gas exchange data were collected from 77 men >6 months after acute myocardial infarction. The gas exchange anaerobic threshold was determined by analysis of the $\dot{V}CO_2$ vs $\dot{V}O_2$ curve below a respiratory exchange ratio of 1.00 using a computerized algorithm. Results demonstrate that this ATge method correlates well with the lactate acidosis threshold, is reproducible, and should be useful as an objective measure of submaximal exercise performance.

EDITORIALS

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Hemodynamic Shear Force in Rupture of Coronary Arterial Atherosclerotic Plaques

S. David Gertz and William C. Roberts

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Stepped-Down Therapy Versus Intermittent Therapy in Systemic Hypertension

Frank A. Finnerty, Jr.

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A 50-Year-Old Useful Report on Coronary Risk for Noncardiac Surgery

Nanette K. Wenger

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Perioperative Myocardial Ischemia and Infarction

Simon Dack

BRIEF REPORTS

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Ages at Death and Sex Distribution in Age Decade in Fatal Coronary Artery Disease

William C. Roberts, Amy H. Kragel, and Benjamin N. Potkin

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Relation of Angiographic Detected Intracoronary Thrombus and Silent Myocardial Ischemia in Unstable Angina Pectoris

Anatoly Langer, Michael R. Freeman, and Paul W. Armstrong

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Effects of Intracoronary Ergonovine on the Contralateral Coronary Artery in Patients with Atypical Chest Pain

Charles R. Lambert, Hendrik du T. Theron, and Carl J. Pepine

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Hypercholesterolemia After Cardiac Transplantation in Children

Karen Uzark, Dennis Crowley, Louise Callow, and Edward Bove

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Atrioventricular Nodal Reentry and Dual Atrioventricular Node Physiology in Patients Undergoing Accessory Pathway Ablation

Marco Zardini, James W. Leitch, Gerard M. Guiraudon, George J. Klein, and Raymond Yee

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Significance of Exercise-Induced Left Hemiblock

Dany M. Marcadet, Philippe Genet, Patrick Assayag, and Paul E. Valère

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Effects of Encainide and Metabolizer Phenotype on Ventricular Conduction During Exercise

Dean G. Karalis, Charles Nydegger, R. Stephen Porter, Joseph Carver, Ileana L. Pina, Steven P. Kutalek, and Eric L. Michelson

1396

Effects of Noninvasive Ambulatory Blood Pressure Measuring Devices on Blood Pressure

Geoffrey Brigden, Paul Broadhurst, Peter Cashman, and Edward B. Raftery

READERS' COMMENTS

1400

Training for Intermediate Clinical Lipid Specialists

H. Robert Superko

Ventricular Arrhythmias During Spontaneous Ischemic ST-Segment Depression

Shlomo Stern

Balloon Angioplasty of Native Aortic Coarctations

P. Syamasundar Rao

Postmortem Cardiomyopathy or Postpartum Cardiomyopathy?

Tsung O. Cheng

Correction

FROM THE EDITOR

1402

The Best Antiarrhythmic Agent Will Be a Lipid-Lowering Agent

William C. Roberts

INSTRUCTIONS TO AUTHORS on page 1399

CLASSIFIED ADVERTISING on pages A54, A70

SYMPOSIUM ERRATUM

In the September 25, 1990 issue "A Symposium: Primary and Secondary Prevention of Cardiovascular Disease," two incorrect figures were printed: Figures 2 (page 51C) and 4 (page 52C) in the article "Acebutolol Effects on Lipid Profile" by Harold Schnaper. The correct figures appear below.

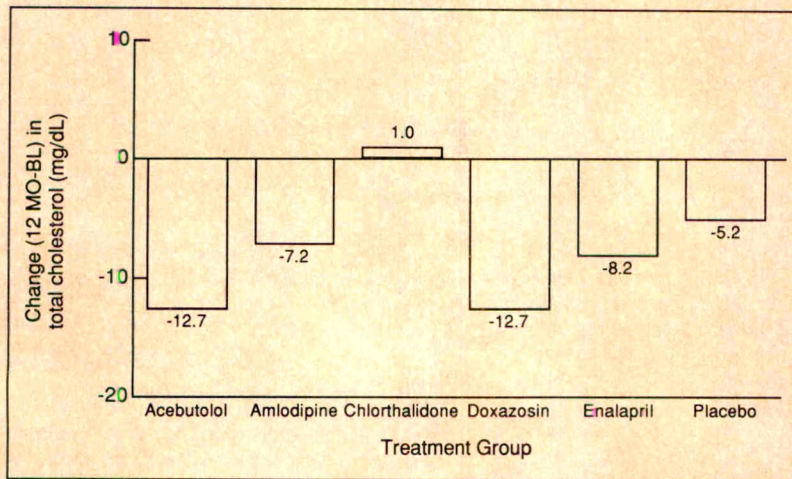


FIGURE 2.

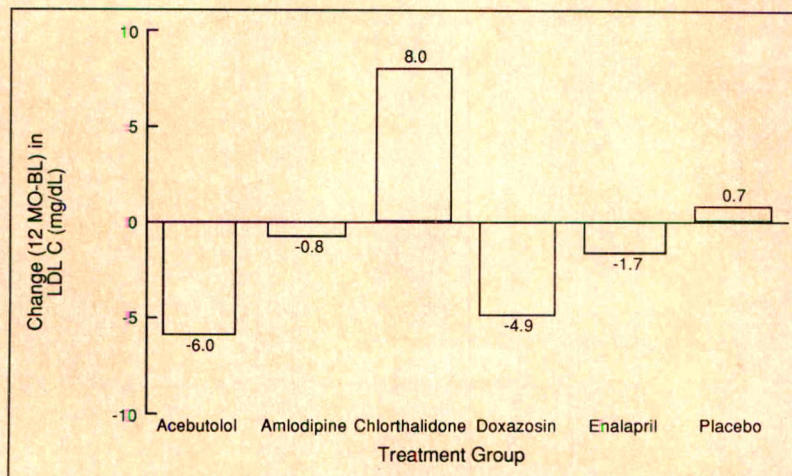
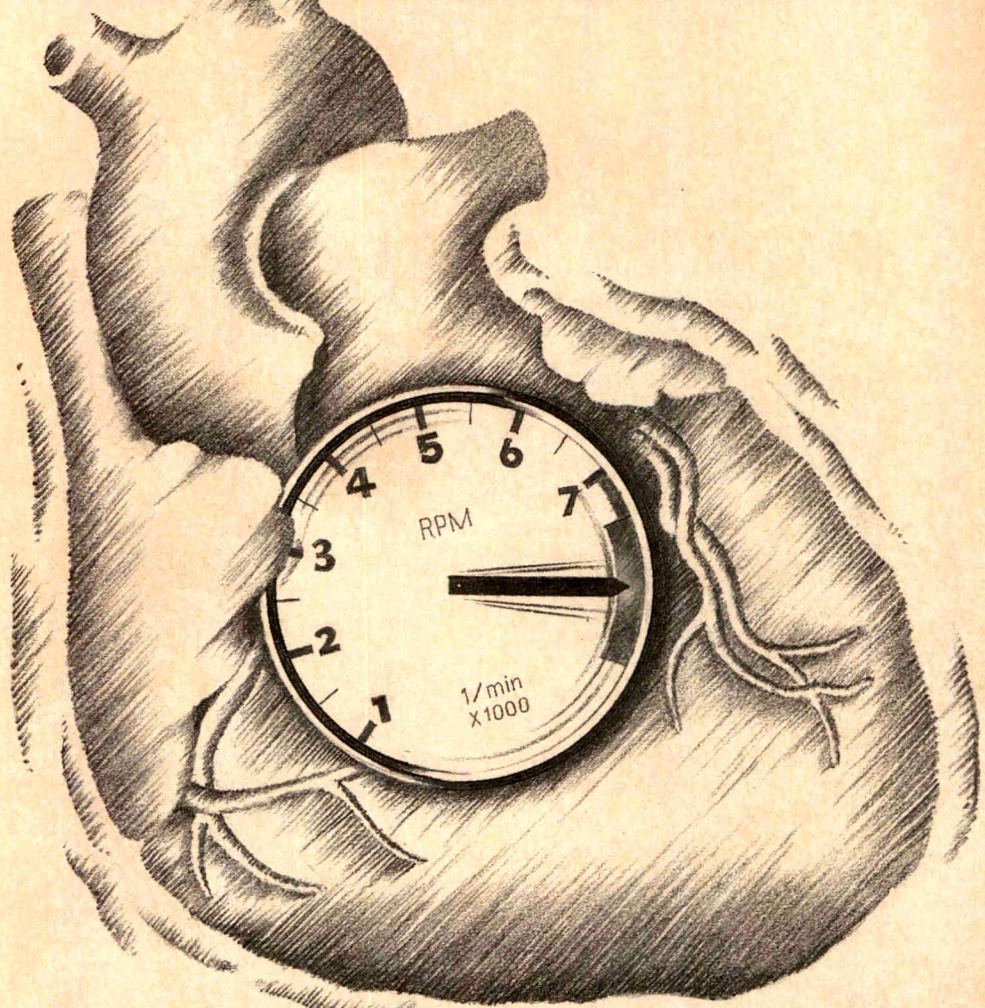


FIGURE 4.

BEYOND THE SYMPTOMS MAY BE SUBSTANCE ABUSE.



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ASK THE QUESTIONS.**

Partnership for a Drug-Free America

CORONARY ARTERY DISEASE

1281**Usefulness of Late Coronary Thrombolysis (Recombinant Tissue-Type Plasminogen Activator) in Preserving Left Ventricular Function in Acute Myocardial Infarction**

Bruno Villari, Federico Piscione, Domenico Bonaduce, Paolo Golino, Torino Lanzillo, Mario Condorelli, and Massimo Chiariello

The effects of recombinant tissue-type plasminogen activator (rt-PA) administration on left ventricular (LV) function and early myocardial expansion in patients with acute myocardial infarction (AMI) were evaluated. Sixty patients were classified into 3 groups: 21 admitted within 4 hours from AMI received rt-PA (group A); 39 admitted 4 to 8 hours after AMI were randomly assigned to rt-PA (group B, n = 19) or conventional therapy (group C, n = 20). LV and coronary angiograms were recorded 8 to 10 days after AMI. The patency rate of the infarct-related vessel was 76% in group A, and 63 and 35% in group B and C, respectively. Significantly lower end-diastolic and end-systolic volume indexes and a smaller number of hypokinetic and akinetic-dyskinetic segments in group A and B than in group C were found. Global and regional (ischemic zone) ejection fractions were greater in groups A and B than in group C. The shortening of the central ischemic zone was significantly higher in group A than in groups B and C. These data confirm the efficacy of early rt-PA administration and suggest that late reperfusion by rt-PA may act beneficially on LV volumes and function.

1287**Usefulness of Antithrombotic Therapy in Resting Angina Pectoris or Non-Q-Wave Myocardial Infarction in Preventing Death and Myocardial Infarction (a Pilot Study from the Antithrombotic Therapy in Acute Coronary Syndromes Study Group)**

Marc Cohen, Philip C. Adams, Linda Hawkins, Matt Bach, and Valentin Fuster

In a prospective pilot trial of antithrombotic therapy in the acute coronary syndromes of resting and unstable angina pectoris or non-Q-wave myocardial infarction, we compared the efficacy of 3 different antithrombotic regimens in the prevention of recurrent ischemic events. Ninety-three consecutive patients were randomized to receive aspirin (325 mg/day), or full-dose heparin followed by warfarin, or the combination of aspirin (80 mg/day) plus heparin and then warfarin. Trial therapy was added to

Continued on page A14



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standardized antianginal medication and was continued for 3 months or until an end point was reached. End points, assessed at 3 months, were recurrent myocardial ischemia, myocardial infarction, death, and major bleeding. During trial therapy, no patient died, had a Q-wave infarction, or a major bleed. However, irrespective of the antithrombotic regimen used, and even with combination therapy, a substantial fraction of patients had recurrent myocardial ischemia and were referred for percutaneous transluminal coronary angioplasty or for coronary artery bypass grafting. Antithrombotic therapy, coupled with early intervention after recurring myocardial ischemia, is associated with a low rate of death or infarction within the first 3 months.

1293

Angiographic Progression to Total Coronary Occlusion in Hyperlipidemic Patients After Acute Myocardial Infarction

Joe K. Bissett, William L. Ngo, Richard P. Wyeth, John P. Matts, and the POSCH Group

The progression of coronary artery stenosis to total occlusion was assessed in 413 hyperlipidemic patients with a history of myocardial infarction. A new finding of total occlusion occurred in 4% (30 of 748) and 7% (40 of 605) of coronary artery segments at 3 and 5 years, respectively. Lesions of >60% became occluded more frequently at both 3 and 5 years ($p < 0.001$). If the risk of progression to total occlusion was determined for the right, left circumflex and left anterior descending coronary arteries, the right coronary artery showed the greatest risk of progression to occlusion by 5 years ($p < 0.02$). Serum triglycerides and total cholesterol were also associated with progression to total occlusion by 5 years.

1298

The Western Washington Myocardial Infarction Registry and Emergency Department Tissue Plasminogen Activator Treatment Trial

Ralph Althouse, Charles Maynard, Manuel D. Cerqueira, Michele Olsufka, James L. Ritchie, and J. Ward Kennedy

During 1 year, 1,028 patients with acute myocardial infarction (AMI) were evaluated for eligibility for thrombolytic therapy; 221 (22%) were eligible: 175 (79%) were correctly identified by emergency physicians and 160 (72%) were enrolled. Only 3 treated patients (2%) did not have documented AMI. Patients ($n = 807$, 78%) were not eligible because of nondiagnostic electrocardiograms (36%), contraindications to thrombolytic therapy (33%), age >75 years or presentation >6 hours from symptom onset (10%). Initial management of AMI with recombinant tissue plasminogen activator in the emergency department provided rapid and safe treatment. Up to 33% of AMI patients could be treated if age >75 and >6 hours of chest pain were not considered restrictions to treatment.

Continued on page A18

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1304

Ability of Calcium-Entry Blockade by Felodipine to Disclose Different Pathogenetic Mechanisms Behind Hyperventilation-Induced Myocardial Ischemia in Men

Diego Ardissino, Stefano Savonitto, Paola Zanini, Paolo Barberis, Stefano De Servi, Alberto Rolla, and Giuseppe Specchia

To verify that hyperventilation-induced myocardial ischemia occurring during either overbreathing or recovery is based on different pathogenetic mechanisms, we investigated the effects of the vasoselective calcium antagonist felodipine in 27 patients with a positive response to a hyperventilation test and with angiographically proven coronary artery disease. Fifteen patients showed ST-segment depression during overbreathing and 12 patients showed ST-segment depression during recovery. According to a double-blind, crossover design, we administered oral felodipine or placebo on 2 consecutive days and compared their effects on hyperventilation-induced myocardial ischemia and on coronary circulation. Felodipine did not modify the ischemia occurring during overbreathing, which was due to an increased oxygen demand, but it completely inhibited ischemia occurring during recovery, which was due to coronary vasoconstriction. This study gives both direct and indirect evidence of the double pathogenetic mechanism behind hyperventilation-induced myocardial ischemia.

1309

Long-Term Prognosis of Myocardial Ischemia Detected by Holter Monitoring in Peripheral Vascular Disease

Khether E. Raby, Lee Goldman, E. Francis Cook, Joanna Rumerman, Joan Barry, Mark A. Creager, and Andrew P. Selwyn

To assess the long-term prognostic significance of myocardial ischemia, as measured by ambulatory electrocardiographic monitoring, we prospectively studied 176 eligible patients scheduled for elective peripheral arterial vascular surgery. Thirty-two patients (18%) had a total of 75 episodes of ischemia. During a mean follow-up period of 615 days, 12 events occurred in 32 patients with ischemia (38%), including 6 cardiac deaths and 6 myocardial infarctions, and in 10 of 144 patients without ischemia (7%), including 3 cardiac deaths and 7 infarctions (risk ratio 5.4, 95% confidence interval 2.6 to 11.4). In a multivariate Cox proportional-hazards model, the presence of ischemia was the only independent predictor of outcome. In patients with peripheral vascular disease, who often are unable to perform adequate exercise testing, ambulatory monitoring for myocardial ischemia is a significant independent predictor of long-term prognosis.

1314

Usefulness of Tomographic Thallium-201 Imaging for Detection of Restenosis After Percutaneous Transluminal Coronary Angioplasty

Harvey S. Hecht, Richard E. Shaw, Thomas R. Bruce, Colman Ryan, Simon H. Stertzer, and Richard K. Myler

The role of tomographic thallium-201 exercise imaging in the detection of restenosis after percutaneous transluminal coronary angioplasty (PTCA)

Continued on page A24

Rythmol

propafenone HCl

150 mg and 300 mg scored tablets

INDICATIONS AND USAGE

RYTHMOL (propafenone HCl) is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician, are life threatening. Because of the proarrhythmic effects of RYTHMOL, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. The use of RYTHMOL is not recommended for use in patients with less severe ventricular arrhythmias, even if the patients are symptomatic. Use of RYTHMOL for the treatment of sustained ventricular tachycardia, like other antiarrhythmics, should be initiated in the hospital.

CONTRAINDICATIONS

RYTHMOL (propafenone HCl) is contraindicated in the presence of uncontrolled congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation and/or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, manifest electrolyte imbalance, and known hypersensitivity to the drug.

WARNINGS

Mortality: In the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double blind study in patients with asymptomatic non life threatening ventricular ectopy who had a myocardial infarction more than six days but less than two years previously and demonstrated mild to moderate left ventricular dysfunction, an excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to carefully matched placebo treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months. The applicability of these results to other populations (e.g., those without recent myocardial infarction and to other antiarrhythmic drugs) is uncertain, but at present it is prudent (1) to consider any IC agent (especially one documented to provoke new serious arrhythmias) to have a similar risk and (2) to consider the risks of Class IC agents, coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life threatening, symptoms or signs.

Proarrhythmic Effects

RYTHMOL, like other antiarrhythmic agents, may cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., tachycardia that is more sustained or more rapid which may lead to fatal consequences. It is therefore essential that each patient given RYTHMOL be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to RYTHMOL (propafenone HCl) supports continued treatment. Overall in clinical trials with propafenone, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had a worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias, which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see above) suggests that an increased risk is present throughout treatment.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE PROPAPENONE or other agents with beta adrenergic blocking activity.

Congestive Heart Failure

During treatment with oral propafenone in patients with depressed baseline function (mean EF=33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients; of those 0.9% were considered probably or definitely related to RYTHMOL. Of the patients with congestive heart failure probably related to propafenone, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to RYTHMOL developed rarely (<0.2%) in patients who had no previous history of CHF. As RYTHMOL exerts both beta blockade and a (dose related) negative inotropic effect on cardiac muscle, patients with congestive heart failure should be fully compensated before receiving RYTHMOL. If congestive heart failure worsens, RYTHMOL should be discontinued (unless congestive heart failure is due to the cardiac arrhythmia) and, if indicated, restarted at a lower dosage only after adequate cardiac compensation has been established.

Conduction Disturbances

RYTHMOL slows atrioventricular conduction and also causes first degree AV block. Average PR interval prolongation and increases in QRS duration are closely correlated with dosage increases and concomitant increases in propafenone plasma concentrations. The incidence of first degree, second degree, and third degree AV block observed in 2,127 patients was 2.5%, 0.6%, and 0.2%, respectively. Development of second or third degree AV block requires a reduction in dosage or discontinuation of RYTHMOL. Bundle branch block (1.2%) and intraventricular conduction delay (1.1%) have been reported in patients receiving propafenone. Bradycardia has also been reported (1.5%). Experience in patients with sick sinus node syndrome is limited and these patients should not be treated with propafenone.

Effects on Pacemaker Threshold

RYTHMOL may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

Hematologic Disturbances

One case of agranulocytosis with fever and sepsis, probably related to use of propafenone, was seen in U.S. clinical trials. The agranulocytosis appeared after 8 weeks of therapy. Propafenone therapy was stopped and the white count had normalized by 14 days. The patient recovered. In the course of over 800,000 patient years of exposure during marketing outside the U.S. since 1978, seven additional cases have been reported. In one of these, concomitant captopril, a drug known to cause agranulocytosis, was used. Unexplained fever and/or decrease in white cell count, particularly during the first three months of therapy, warrant consideration of possible agranulocytosis/granulocytopenia. Patients should be instructed to promptly report the development of any signs of infection such as fever, sore throat, or chills.

PRECAUTIONS

Hepatic Dysfunction:

Propafenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. The dose of propafenone given to patients with impaired hepatic function should be significantly reduced. Careful monitoring for excessive pharmacological effects (see OVERDOSAGE) should be carried out.

Renal Dysfunction:

A considerable percentage of propafenone metabolites (18.5%-38% of the dose/48 hours) are excreted in the urine. Until further data are available, RYTHMOL should be administered

cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (see OVERDOSAGE).

Elevated ANA Titers:

Positive ANA titers have been reported in patients receiving propafenone. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

Impaired Spermatogenesis:

Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose intravenous administration. Evaluation of the effects of short term propafenone administration on spermatogenesis in 11 normal subjects suggests that propafenone produced a reversible, short term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving propafenone chronically have suggested no effect of propafenone on sperm count.

Drug Interactions: Quinidine: Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers. There is, as yet, too little information to recommend concomitant use of propafenone and quinidine. **Local Anesthetics:** Concomitant use of local anesthetics may increase the risks of central nervous system side effects. **Digitalis:** RYTHMOL produces dose related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day propafenone without affecting digoxin renal clearance. Digoxin dosage should ordinarily be reduced when propafenone is started. **Beta-Antagonists:** Propafenone appears to inhibit the hydroxylation pathway for propranolol and metoprolol (just as quinidine inhibits propafenone metabolism).

While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone. **Warfarin:** In a study of eight healthy subjects receiving propafenone and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary. **Cimetidine:** Concomitant administration of propafenone and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone.

Other: Limited experience with propafenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Life time maximally tolerated oral dose studies in mice (up to 360 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propafenone. RYTHMOL was not mutagenic when assayed for genotoxicity. **Pregnancy Teratogenic Effects:** Pregnancy Category C: Propafenone has been shown to be embryotoxic in rabbits and rats when given in doses 10 and 40 times, respectively, the maximum recommended human dose. No teratogenic potential was apparent in either species. There are no adequate and well controlled studies in pregnant women. Propafenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Pregnancy Nonteratogenic Effects:** In a perinatal and postnatal study in rats, propafenone, at dose levels of 6 or more times the maximum recommended human dose, produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development.

Labor and Delivery: It is not known whether the use of propafenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from RYTHMOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of RYTHMOL in children has not been established. **Geriatric Use:** There do not appear to be any age-related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, RYTHMOL should be used with caution. The effective dose may be lower in these patients.

ADVERSE REACTIONS
Adverse reactions associated with RYTHMOL (propafenone HCl) occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. About 20% of patients discontinued due to adverse reactions.

Adverse reactions reported for $\geq 1\%$ of 2,127 patients who received propafenone in U.S. clinical trials are presented in the following list. Dizziness, Nausea and/or Vomiting, Unusual Taste, Constipation, Fatigue, Dyspnea, Proarrhythmia, Angina, Headache(s), Blurred Vision, CHF, Ventricular Tachycardia, Dyspepsia, Palpitations, Rash, First Degree AV Block, Diarrhea, Weakness, Dry Mouth, Syncope/Near Syncope, Increased QRS Duration, Chest Pain, Anorexia, Abdominal Pain/Cramps, Ataxia, Insomnia, Premature Ventricular Contraction(s), Bradycardia, Anxiety, Edema, Tremor(s), Diaphoresis, Bundle Branch Block, Drowsiness, Atrial Fibrillation, Flatulence, Hypotension, Intraventricular Conduction Delay, Joint(s) Pain. In addition, the following adverse reactions were reported less frequently than 1% either in clinical trials or in marketing experience (*adverse events for marketing experience are given in italics*). Causality and relationship to propafenone therapy can not necessarily be judged from these events. **Cardiovascular System:** Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia. **Nervous System:** Abnormal dreams, abnormal speech, abnormal vision, *apnea*, *coma*, confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo. **Gastrointestinal:** A number of patients with liver abnormalities associated with propafenone therapy have been reported in foreign postmarketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were, simply discovered through clinical chemistries, others because of clinical symptoms. One case was rechallenged with a positive outcome. Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), gastroenteritis, hepatitis (0.03%) **Hematologic:** Agranulocytosis, anemia, bruising, granulocytopenia, *increased bleeding time*, leukopenia, purpura, thrombocytopenia. **Other:** Alopecia, eye irritation, *hyponatremia/inappropriate ADH secretion*, impotence, increased glucose, *kidney failure*, positive ANA (0.7%), *lupus erythematosus*, muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus.

OVERDOSAGE
The symptoms of overdosage, which are usually most severe within 3 hours of ingestion, may include hypotension, somnolence, bradycardia, intraatrial and intraventricular conduction disturbances, and rarely convulsions and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam. General supportive measures such as mechanical respiratory assistance and external cardiac massage may be necessary.

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was evaluated in 116 patients, 61 (53%) with 1-vessel and 55 (47%) with multivessel PTCA, with a total of 185 dilated vessels. Complete revascularization was performed in 89 (77%) and partial revascularization in 27 (23%) of the patients. Restenosis was angiographically demonstrated in 69 (60%) of the patients and in 85 (46%) of the vessels; disease progression in previously normal vessels was noted in 11 patients. Single-photon emission computed tomography detected restenosis with a sensitivity, specificity and accuracy of 93, 77 and 86% for the entire patient group and 86, 86 and 86% in specific vessels with comparable results after 1- or multivessel PTCA and complete or partial revascularization. Disease progression was identified with a sensitivity, specificity and accuracy of 91, 84 and 85%. Single-photon emission computed tomographic thallium-201 imaging is an excellent tool for the detection of restenosis and disease progression after 1- or multivessel PTCA and complete or partial revascularization.

1319

Coronary Artery Disease in the Octogenarian: Angiographic Spectrum and Suitability for Revascularization

Glen J. Kowalchuk, Samuel C. Siu, and Stanley M. Lewis

The coronary angiographic findings of 84 octogenarians presenting with severe or unstable angina were examined to assess the extent of coronary artery disease as well as suitability for both coronary artery bypass surgery and coronary angioplasty. The frequency of 0-, 1-, 2- and 3-vessel and left main coronary artery disease was 7, 14, 21, 57 and 13%, respectively. Based on angiographic findings, coronary artery bypass surgery and coronary angioplasty were feasible in 88 and 31% of patients, respectively. Revascularization procedures were associated with significant morbidity and mortality in this patient group.

1324

Prevalence and Correlates of Increased Lung/Heart Ratio of Thallium-201 During Dipyridamole Stress Imaging for Suspected Coronary Artery Disease

Flordeliza S. Villanueva, Sanjiv Kaul, William H. Smith, Denny D. Watson, Shailendra K. Varma, and George A. Beller

The clinical characteristics and thallium-201 findings were correlated with lung/heart thallium-201 ratio in 87 patients undergoing dipyridamole thallium-201 stress testing. Nineteen patients (22%) had an elevated ratio (>0.51) that was associated with a prior infarction, β -blocker therapy and lower rate-pressure product after dipyridamole infusion. It was also associated with a greater likelihood of initial, redistribution and persistent defects, as well as left ventricular cavity dilatation on thallium-201 imaging ($p < 0.05$). Multivariate analysis demonstrated that the presence of redistribution and left ventricular cavity dilatation were the most significant correlates of lung/heart thallium-201 ratio. As with exercise thallium-201 imaging, therefore, increased pulmonary thallium-201 uptake may be a marker of functionally more significant coronary artery disease.

Continued on page A30

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1329

Sudden Death Behind the Wheel from Natural Disease in Drivers of Four-Wheeled Motorized Vehicles

David H. Antecol and William C. Roberts

The heart was studied in 30 persons who died suddenly from natural causes in the driver's seat of an automobile, truck or bus. Twenty had cardiac arrest while driving and the other 10 while sitting in the driver's seat of a parked vehicle. Of the 20 drivers, 16 died from atherosclerotic coronary artery disease (CAD). Of the 16 with fatal CAD, an average of 2.3 ± 0.8 of the 4 major coronary arteries were narrowed $>75\%$ in cross-sectional area by plaque. The remaining 4 drivers died from noncoronary conditions. The other 10 were found dead in the driver's seat of a parked vehicle and 8 of them had fatal CAD. Victims dying suddenly from CAD while driving are similar to other out-of-hospital sudden coronary death victims with respect to mean age, gender, heart weight, frequency of healed myocardial infarcts, number of major epicardial coronary arteries severely narrowed, and the percentage of 5-mm-long segments of the major coronary arteries narrowed by atherosclerotic plaque.

SYSTEMIC HYPERTENSION

1336

Changes in Plasma Free Fatty Acids and Glycerols During Prolonged Exercise in Trained and Hypertensive Persons Taking Propranolol and Pindolol

Jacquelyn K. Jesek, Nicholas B. Martin, Craig E. Broeder, Evan L. Thomas, Kathleen C. Wambsgans, Zandrie Hofman, John L. Ivy, and Jack H. Wilmore

The extent to which lipolysis is attenuated at prolonged submaximal exercise during therapy with β blockade was determined in 12 normotensive endurance-trained and 12 hypertensive sedentary men using drugs with and without intrinsic sympathomimetic activity (ISA). Subjects performed a graded treadmill test to determine maximal oxygen uptake ($\dot{V}O_{2\max}$). This was followed by 2-hour walks at 25 and 45% of each subject's $\dot{V}O_{2\max}$ under each of 3 treatments: pindolol (ISA), propranolol (non-ISA) and placebo. The distribution of medication was randomized and double-blinded. Blood samples taken at rest and every 30 minutes during the 2-hour walks were analyzed to determine the concentrations of free fatty acids and glycerol. Beta-adrenergic blockade did not attenuate lipolysis in the untrained hypertensive subjects when compared with results during placebo administration. However, β blockade tended to attenuate lipolysis in the trained normotensive subjects when compared with results during placebo therapy. No differences between pindolol and propranolol were observed.

Continued on page A33

1342

Effects of Renin Inhibition in Systemic Hypertension

Pamela W. Anderson, Yung S. Do, Morris Schambelan, Richard Horton, Robert S. Boger, Robert R. Luther, and Willa A. Hsueh

The effects of the direct renin inhibitor enalkiren (Abbott Laboratories) on blood pressure, the renin-angiotensin-aldosterone system, and urinary prostacyclin were examined in 8 healthy patients with essential hypertension. With an unrestricted sodium diet, plasma renin concentration was rapidly inhibited, mean arterial blood pressure and plasma aldosterone concentration declined progressively, plasma immunoreactive active renin concentration increased progressively, and urinary excretion of the stable metabolite of prostacyclin (6-keto-PGF_{1α}) did not change significantly. The addition of a diuretic for 1 week decreased baseline blood pressure and increased baseline plasma renin and aldosterone values, but responses to enalkiren were not significantly different from those observed before diuretic administration. Enalkiren is effective in lowering blood pressure and in inhibiting the renin system, without altering urinary prostacyclin excretion, in patients with essential hypertension. These results suggest that the renin system contributes to the maintenance of elevated blood pressure in some patients with essential hypertension.

CONGESTIVE HEART FAILURE

1348

Importance of Hemodynamic Response to Therapy in Predicting Survival with Ejection Fraction $\leq 20\%$ Secondary to Ischemic or Nonischemic Dilated Cardiomyopathy

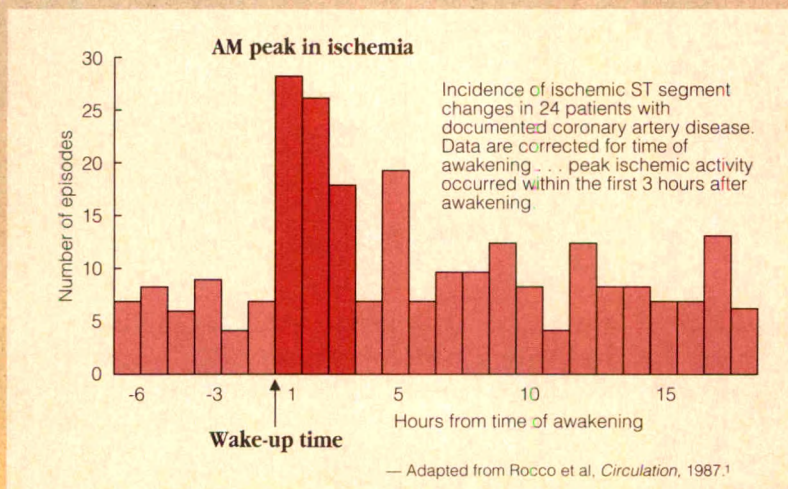
Lynne Warner Stevenson, Jan H. Tillisch, Michele Hamilton, Michael Luu, Catherine Chelimsky-Fallick, Jaime Moriguchi, Jon Kobashigawa, and Julie Walden

To identify patients with ejection fractions $\leq 20\%$ who are likely to survive on tailored medical therapy after referral to transplantation, 152 patients were studied before and after therapy with vasodilators and diuretics tailored to hemodynamic goals. Despite initial average ejection fraction of 0.15, cardiac index of 2.0 liters/min/m² and pulmonary artery wedge pressure of 28 mm Hg, actuarial survival during tailored therapy for 152 patients was 63% at 1 year. Survival was unrelated to initial filling pressure elevation, but was best predicted by response to therapy, such that patients achieving pulmonary wedge pressure ≤ 16 mm Hg demonstrated having 1-year survival of 83 vs 38% ($p = 0.0001$). Serum sodium and the presence of coronary artery disease were also independently predictive. Although survival with ejection fraction $\leq 20\%$ is better than previously described, early transplantation should be considered when ventricular filling pressures cannot be adequately decreased, particularly if coronary artery disease is present.

Continued on page A37

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VALVULAR HEART DISEASE

1355**Use of Auscultation to Follow Patients with Mitral Systolic Clicks and Murmurs**

Oswald B. Tofler and Geoffrey H. Tofler

To determine the clinical significance of an auscultatory classification of mitral systolic clicks with or without murmurs, the medical records of 291 patients with these signs were reviewed. Patients were divided into (1) single or multiple apical systolic clicks with no murmur ($n = 99$); (2) single or multiple apical systolic clicks and a late systolic murmur ($n = 129$); and (3) single or multiple apical clicks associated with an apical pansystolic murmur or murmur beginning in the first half of systole ($n = 63$). During follow-up (mean 8 years), 2 cardiac-related deaths occurred: 1 each in classes 1 and 2. Mitral valve surgery was required in 3 class 2 patients (2%) and in 2 class 3 patients (3%). No class 1 patient developed severe mitral regurgitation or required surgery. Auscultatory findings assisted in the explanation and relief of anxiety regarding palpitations, a major indication for cardiologic referral. For patient management, the use of an auscultatory-derived classification may be preferable to the technically generated "mitral valve prolapse."

MISCELLANEOUS

1359**Quantitative Analysis of Ventricular Late Potentials in Healthy Subjects**

Angelo A. Raineri, Marcello Traina, Antonino Rotolo, and Renzo M. R. Lombardo

Few studies have been conducted in healthy subjects to assess normal values for signal-averaging electrocardiography. Sixty-one healthy subjects were enrolled in our study (33 men, 28 women). The results (mean \pm standard deviation) are as follows: duration of the filtered QRS (QRS duration) was 95 ± 10 ms; duration of the low-amplitude signals (LAS) in the terminal portion of QRS $<40 \mu\text{V}$ (LAS <40) was 32 ± 8 ms; and root-mean-square voltage in the last 40 ms (RMS-40) was $33 \pm 16 \mu\text{V}$. A significant difference was noted in QRS duration between men and women (98 ± 11 vs 92 ± 6 ms, $p = 0.006$); however, no difference was found in LAS <40 (31 ± 8 vs 34 ± 8 ms) and in RMS-40 (36 ± 17 vs $30 \pm 13 \mu\text{V}$). QRS duration confidence limits of 95% were ≤ 114 ms for the total group, ≤ 120 ms for men and ≤ 104 ms for women. Normalization of QRS duration for height (normal value <66 ms/m) eliminated any difference between men and women. LAS <40 had an upper value of 48 ms in the total group, 46 ms in men and 50 ms in women. It was not possible to define normal values for RMS-40 because of the wide range of 95% limits of confidence. Adoption of criteria that are related either to gender or to body characteristics (QRS duration normalized for height) is warranted on the basis of this study.

Continued on page A40

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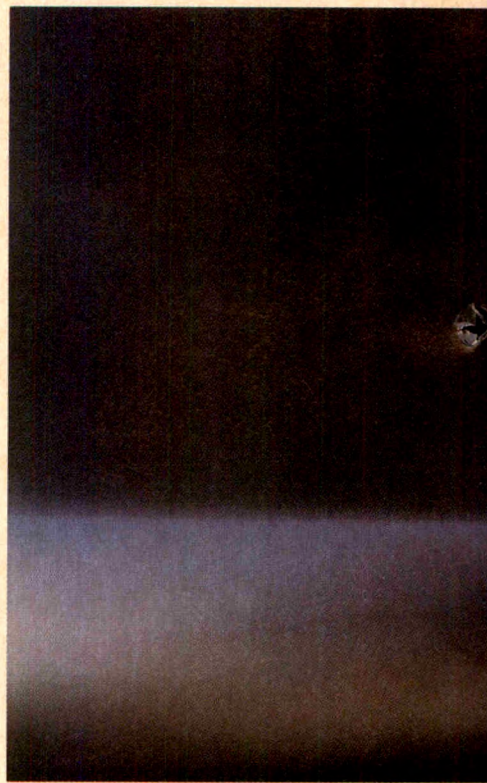
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Validation of a Computerized Technique for Detection of the Gas Exchange Anaerobic Threshold in Cardiac Disease

Kenneth Dickstein, Stale Barvik, Torbjorn Aarsland, Steven Snapinn, and Jay Millerhagen

Maximal cardiopulmonary exercise was performed in 77 men after myocardial infarction. The gas exchange anaerobic threshold (ATge) was determined by analysis of the carbon dioxide elimination versus oxygen consumption plot using a computerized algorithm. The mean \pm standard deviation (SD) oxygen consumption ($\dot{V}O_2$) for the ATge was 905 ± 220 vs 866 ± 299 ml/min for the lactate acidosis threshold ($r = 0.86$, $p < 0.001$). Mean \pm SD $\dot{V}O_2$ at the ATge for test 1 was 968 ± 225 vs 952 ± 217 ml/min for test 2 ($r = 0.71$, $p < 0.001$). Mean \pm SD peak $\dot{V}O_2$ was $1,392 \pm 379$ vs 912 ± 202 ml/min at the ATge ($r = 0.76$, $p < 0.001$). The results demonstrate that this ATge method correlates well with the lactate threshold, is reproducible and should be useful as an objective measure of submaximal exercise performance.

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Usefulness of Late Coronary Thrombolysis (Recombinant Tissue-Type Plasminogen Activator) in Preserving Left Ventricular Function in Acute Myocardial Infarction

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This study assesses whether administration of recombinant tissue-type plasminogen activator (rt-PA) up to 8 hours after onset of symptoms of acute myocardial infarction (AMI) may result in a significant improvement in left ventricular function. Sixty patients were classified into 3 groups: group A (n = 21) received rt-PA within 4 hours from symptom onset; the remaining 39 patients, admitted between 4 and 8 hours, were randomized into 2 groups—group B (n = 19) received rt-PA, and group C (n = 21) was treated with conventional therapy. Coronary and left ventricular angiograms were recorded 8 to 10 days after rt-PA administration. The patency rate of the infarct-related artery was 76% in group A, and 63 and 35% in group B and C, respectively. The Thrombolysis in Myocardial Infarction trial perfusion grade was higher in group A and B than in group C (A vs C: $p < 0.005$; B vs C: $p < 0.01$). Left ventricular ejection fraction was significantly higher in group A ($60.2 \pm 10\%$) and B ($54.7 \pm 12\%$) compared with group C ($44.2 \pm 12\%$) (A vs C: $p < 0.01$; B vs C: $p < 0.05$). Regional wall motion of the entire ischemic zone was better in group A and B than in group C (A vs C: $p < 0.001$; B vs C: $p < 0.01$). In contrast, the kinesis of the central ischemic zone was significantly better in group A than in both group B and C (A vs B: $p < 0.05$; A vs C: $p < 0.001$).

The number of hypokinetic, akinetic and dyskinetic segments were lower in group A and B than in group C (A vs B: $p < 0.01$, B vs C: $p < 0.05$ and A vs C: $p < 0.01$ and B vs C: $p < 0.01$, respectively). Thus, these data confirm the efficacy of early thrombolysis and suggest that late reperfusion may act beneficially in preserving left ventricular volumes and function.

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Early coronary thrombolysis is considered the treatment of choice for most patients with acute myocardial infarction (AMI), because this procedure may result in improvement in left ventricular function and reduction of in-hospital and long-term mortality.^{1–9} However, some controversy still exists with regard to the efficacy of thrombolytic therapy administered relatively late after the onset of symptoms.⁹ Several experimental studies have demonstrated that the extent of ischemic myocardium ultimately undergoing necrosis is dependent on the duration of the ischemic period and that reperfusion does not usually result in any appreciable myocardial salvage after 3 to 4 hours.^{10,11} However, most patients sustaining AMI may have developed collateral vessels that could have prolonged the time span before irreversible cellular damage occurred.^{7,12,13}

Based on these considerations, the present study assessed whether coronary thrombolysis performed between 4 and 8 hours from symptom onset would act beneficially on left ventricular function in patients with AMI. To accomplish this goal, we compared the effects of late thrombolysis on left ventricular function with those of conventional therapy in patients admitted 4 to 8 hours from the onset of chest pain. Furthermore, we compared these 2 groups with a third group of patients with AMI treated with single chain recombinant tissue-type plasminogen activator (rt-PA) earlier in the course of infarction (i.e., <4 hours from symptom onset).

METHODS

Patients: All patients admitted to our coronary care unit between January 1989 and October 1989 with a diagnosis of AMI revealed within 8 hours were considered for entry into this study. The diagnosis was established on the basis of typical chest pain and ST-segment elevation of ≥ 0.2 mV in a precordial lead or 0.1 mV in a limb lead. Exclusion criteria were: history of myocardial infarction, any major hemorrhage or stroke in the previous 6 months, major injury or surgery in the previous 6 weeks, cardiopulmonary resuscitation performed on admission to the hospital, severe arterial hypertension (systolic blood pressure >220 mm Hg), or active peptic ulcer. Sixty-nine patients entered this study but only 60 completed the study protocol. Nine patients

TABLE I Patient Characteristics

	rt-PA <4 hrs	rt-PA 4-8 hrs	Control Subjects
Patients (no.)	21	19	20
Age (yrs)	51 ± 8	52 ± 9	53 ± 8
Peak creatine kinase (mU/liter)	3,074 ± 1,764	2,749 ± 1,678	2,890 ± 1,651
Time to peak creatine kinase (hours)	11 ± 5	16 ± 5*	21 ± 7†
Time of intervention (min) (range)	145 ± 58 (30-220)	360 ± 61 (290-430)	358 ± 58 (250-430)
Anterior AMI (no.)	12	10	11
Inferior AMI (no.)	9	9	9
Time to coronary angiography (days)	9.1 ± 0.7	9.1 ± 0.7	9.2 ± 0.7
1-vessel CAD (no.)	9	8	10
TIMI grade	2.09 ± .83‡	1.78 ± .84§	0.85 ± 0.93

* A vs B, $p < 0.05$; † A vs C, $p < 0.01$; ‡ A vs C, $p < 0.005$; § B vs C, $p < 0.01$
 AMI = acute myocardial infarction; CAD = coronary artery disease; rt-PA = recombinant tissue-type plasminogen; TIMI = Thrombolysis in Myocardial Infarction trial.

were excluded: 6 refused cardiac catheterization, 1 had a cerebral hemorrhage and underwent successful surgery, 1 patient had another AMI during hospitalization and 1 died from cardiogenic shock. These latter events occurred before the time of catheterization.

All consecutive patients admitted to the coronary care unit within 4 hours from the onset of chest pain received rt-PA intravenously (10 mg bolus followed by an infusion of 50 mg over 1 hour and then 20 mg/hour over the next 2 hours) (group A, $n = 21$). Thirty-nine patients admitted to the coronary care unit between 4 and 8 hours from onset of chest pain were randomly assigned to a group treated with rt-PA at the same dose as previously described (group B, $n = 19$) and to a group treated only with conventional therapy (intravenous nitroglycerin and oral nifedipine) (group C, $n = 20$) (Table I). All patients received conventional therapy and a bolus of 10,000 U of heparin at the time of rt-PA administration, followed by an infusion of 1,000 U/hour and adjusted thereafter to maintain the activated partial thromboplastin time between 1.5 and 2 times the upper limit of normal. Heparin therapy was continued

in the absence of serious hemorrhage, until coronary angiography was performed. Blood was sampled for serum creatine kinase immediately after admission and then every 3 to 6 hours over the next 24 hours and every 12 to 24 hours up to 72 hours. Eight to 10 days after admission, all patients underwent right- and left-sided cardiac catheterization and coronary angiography. The infarct-related artery was localized by: (1) ST-segment elevation on the electrocardiogram; (2) hypokinetic wall motion on the ventriculograms; (3) residual stenosis or thrombotic material, or both, in the coronary artery.

Left ventriculography was performed in the 30° right anterior oblique projection using a powered injection of 40 ml of nonionic contrast medium (iopamidol) through a pigtail catheter. The film speed was 50 frames/s. Calibration of the magnification factor was obtained by filming a square grid placed at the level of the left ventricle. Films were projected by a 35-mm film projector and converted into a video format with a video camera. The contours of the ventricle were traced on a working table by a blinded observer with the aid of a digitizing penlight. All contour data were coded and stored using a PDP 11/34 computer onto a RK-01 disk (Digital Equipment Co.). The intraobserver variability of the method was assessed in a previous study from our laboratory.¹⁴

Left ventricular chamber volumes and global ejection fraction were calculated by the area-length method.¹⁵ Regional wall motion was analyzed by a single observer in 2 different independent cycles free from ventricular ectopy, using a semiautomatic computer-aided system (Digital PDP 11/34) for analysis of ventricular wall motion (AVD Siemens). The left ventricle silhouettes were divided into 90 segments by the radial coordinate method.¹⁶ Regional left ventricular function was evaluated as follows: (1) Fractional shortening was expressed as the mean shortening of segments in the worst 50% of the infarct zone. (2) Hypokinesia was expressed as the number of segments with a wall motion reduction exceeding 2 standard deviations of the normal value determined on left ventriculography in 21 age-matched normal subjects. These patients were suspected of having coronary heart disease, underwent diagnostic cardiac catheterization and were found to have normal cardi-

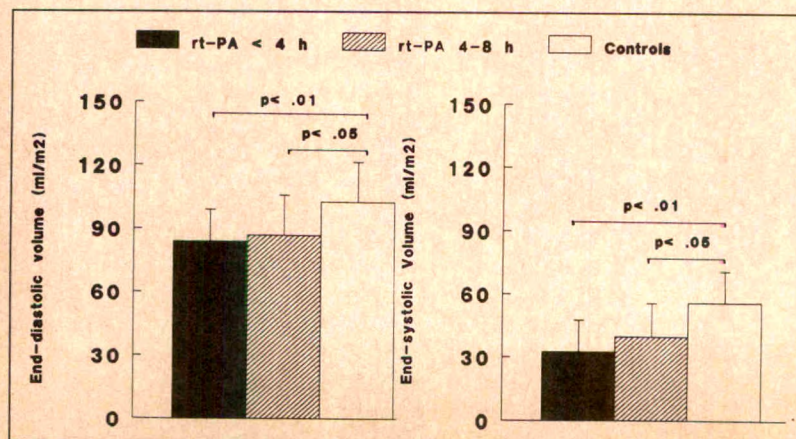


FIGURE 1. Effects of the different treatments on left ventricular volumes: EDVI = end-diastolic volume index; ESVI = end-systolic volume index; rt-PA = recombinant tissue-type plasminogen activator.

ac anatomy, normal coronary arteries and normal ventricular function. (3) Akinesia-dyskinesia was defined as the number of segments with a shortening ≤ 0 (comparing both systolic and diastolic lengthening).

Artery territories were defined by the analysis of 74 patients with no history of thoracotomy or valvular or congenital heart disease, affected by isolated stenoses ($>75\%$) of the left anterior descending or right coronary arteries studied in our laboratory between 1984 and 1988. The region of the left ventricle (segments 10 to 53), in which mean segment motion in the 39 patients with stenosis of the left anterior descending artery was significantly depressed compared with that of a control group without coronary artery disease, was defined as the left anterior descending territory. The territory of the right coronary artery was similarly defined as segments 45 to 80 using the 35 patients with single stenosis of that vessel. The ischemic zone was defined as the segments of the zone supplied by the infarct-related artery. The perinfarcted zone was defined as the 10 segments before and after the ischemic zone. All remaining segments were considered as the noninfarcted zone. The shortening of the ischemic, periischemic and nonischemic zone was also evaluated.

Coronary perfusion was evaluated according to the Thrombolysis in Myocardial Infarction (TIMI) trial grading scale.²

Data are presented as mean \pm standard deviation. One-way analysis of variance was used for statistical evaluation. If a significant F test was found, Student's *t* test for unpaired observation with the Bonferroni's correction was performed to obtain multiple comparisons.

RESULTS

Patient characteristics are listed in Table I.

Hemodynamics and coronary angiography: No significant differences were found among the 3 groups of patients with regard to the hemodynamic variables (Table II). During coronary angiography, patency of the infarct-related vessel (TIMI grade 2 or 3) was found in 16 of 21 patients (76%) in group A, 12 of 19 patients

TABLE II Hemodynamic Variables

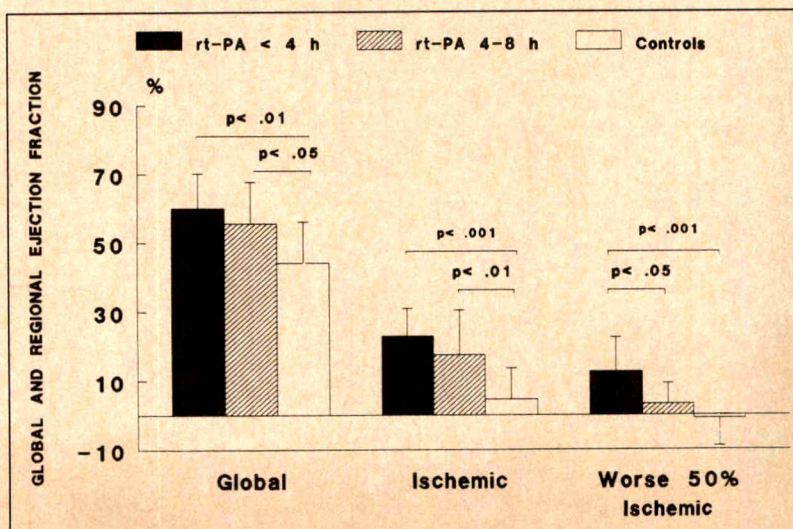
	rt-PA <4 hrs	rt-PA 4-8 hrs	Control Subjects
HR (beats/min)	80 \pm 12	79 \pm 12	88 \pm 11
LVSP (mm Hg)	127 \pm 21	123 \pm 15	134 \pm 19
LVDP (mm Hg)	17 \pm 9	14 \pm 5	18 \pm 8
MAP (mm Hg)	88 \pm 12	92 \pm 11	93 \pm 14
RAP (mm Hg)	4 \pm 4	5 \pm 4	5 \pm 4
MWP (mm Hg)	14 \pm 6	11 \pm 5	14 \pm 7
CI (liters/min/m ²)	2.9 \pm 0.5	2.7 \pm 0.9	2.4 \pm 0.7

CI = cardiac index; HR = heart rate; LVDP = left ventricular diastolic pressure; LVSP = left ventricular systolic pressure; MAP = mean arterial pressure; MWP = mean wedge pressure; RAP = right atrial pressure; rt-PA = recombinant tissue-type plasminogen activator.

(63%) in group B and 7 of 20 patients (35%) in group C. The average TIMI grade was 2.1 ± 0.8 in group A, 1.8 ± 0.8 in group B and 0.9 ± 0.9 in group C (A vs C = $p < 0.005$; B vs C = $p < 0.01$).

Left ventricular analysis: End-diastolic volume index was significantly lower in group A (85 ± 15 ml/m²) and B (88 ± 19 ml/m²) than in group C (103 ± 19 ml/m²) (A vs C = $p < 0.01$; B vs C = $p < 0.05$) (Figure 1). End-systolic volume index was significantly lower in group A (33 ± 15 ml/m²) and B (40 ± 16 ml/m²) than in group C (56 ± 15 ml/m²) (A vs C = $p < 0.01$; B vs C = $p < 0.05$) (Figure 1). Global ejection fraction was significantly higher in patients in group A ($60 \pm 10\%$) and B ($55 \pm 12\%$) than in group C patients ($44 \pm 12\%$) (A vs C = $p < 0.01$; B vs C = $p < 0.05$) (Figure 2). The percent shortening of the ischemic zone was $23 \pm 8\%$ in group A, $18 \pm 14\%$ in group B and $5 \pm 9\%$ in group C (A vs C = $p < 0.001$; B vs C = $p < 0.01$) (Figure 2); the percent shortening of the worst 50% of the infarct zone was significantly higher in group A ($13 \pm 11\%$) than in group B ($3 \pm 7\%$) and group C ($-1 \pm 8\%$) (A vs B = $p < 0.05$; A vs C = $p < 0.001$) (Figure 2). No significant differences were found in shortening of the periischemic zone (21 ± 7 , 20 ± 7 , $16 \pm 7\%$ in group A, B and C, respectively) and nonischemic zone (35 ± 14 , 35 ± 9 , $29 \pm 9\%$ in group A, B and C, respectively).

FIGURE 2. Effects of different recombinant tissue-type plasminogen activator (rt-PA) administration on global and regional ejection fraction: the ejection fraction of the central ischemic zone was significantly higher in the early-treated group (black bars) than in the remaining groups.



The number of hypokinetic segments was significantly lower in group A (14 ± 11 segments) and group B (20 ± 15 segments) than in group C (36 ± 14 segments) (A vs C = $p < 0.01$; B vs C = $p < 0.05$) (Figure 3).

The number of akinetic-dyskinetic segments was significantly lower in group A (1 ± 4) and B (4 ± 6) with respect to group C (14 ± 4) (A vs C = $p < 0.01$; B vs C = $p < 0.01$) (Figure 3). Akinetic-dyskinetic segments were found in 4 of 21 patients (19%) in group A, in 6 of 19 patients (28%) in group B and in 11 of 20 patients (55%) in group C.

DISCUSSION

Our study supports the hypothesis that late thrombolysis may exert a beneficial effect on left ventricular function and reduce end-systolic and end-diastolic volumes.

In both early and late rt-PA-treated groups, we have found a significantly higher ejection fraction with respect to the control group. This was mainly due to an improved motion of the ischemic zone (Figure 2), whereas shortening of the peri- and nonischemic zones was not significantly affected by treatment. The central ischemic zone has shown a higher shortening in group A than in both group B and C, confirming the concept that the earlier reperfusion is achieved, the bigger salvage of ischemic myocardium is obtained. We have also found a lesser extension of hypokinetic and a-dyskinetic segments in groups A and B than in group C, suggesting the continued beneficial effects of thrombolysis performed within 8 hours. The mechanisms leading to these positive effects of thrombolysis, performed both early (< 4 hours) and late (4 to 8 hours), are through a better perfusion of the ischemic zone.¹⁷ In fact, we found a significantly higher TIMI grade and a higher

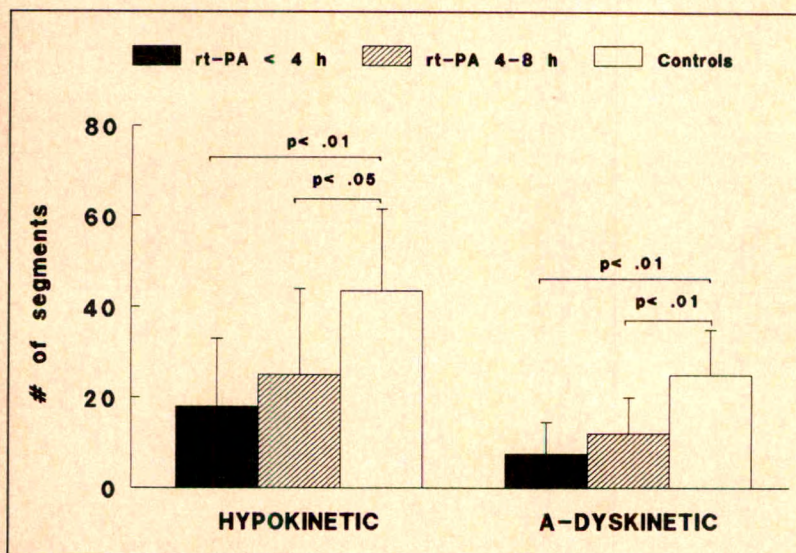


FIGURE 3. In the early-treated group (recombinant tissue-type plasminogen activator [rt-PA] < 4 hours) and in the late-treated group (rt-PA 4 to 8 hours), the number of hypokinetic and akinetic-dyskinetic segments (a-dyskinetic) was significantly lower with respect to the control group.

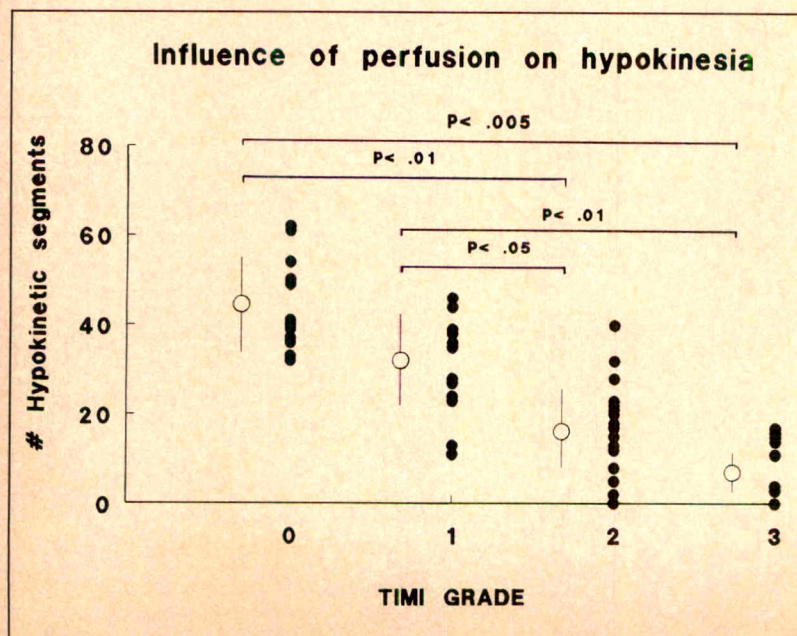


FIGURE 4. Influence of the perfusion grade on the extension of hypokinesia: The higher the Thrombolysis in Myocardial Infarction trial perfusion grade, the fewer the number of hypokinetic segments.

patency rate of the infarct-related artery at 8 to 10 days after myocardial infarction in our rt-PA-treated patients (groups A and B) than in group C patients (Table I). It has been suggested that residual flow through a subtotal lesion extends the time window for myocardial salvage by thrombolytic therapy in a similar way as does residual flow through collateral channels.^{7,12,13} Thus, a better perfusion of the ischemic territories occurring in our group A and B patients compared with group C patients led to the reduction of the extension of hypokinesia and a-dyskinesia with a consequent higher ejection fraction. The importance of the perfusion grade in preserving wall motion of the ischemic zone in our patients is shown in Figure 4, where this effect on the extension of hypokinesia is evident regardless of the treatment arm. Conversely, infarct vessel patency at 8 to 10 days after infarction is not necessarily representative of infarct vessel patency noted immediately after thrombolytic therapy. There is a substantial potential for spontaneous thrombolysis and reocclusion to occur in the interim. One should consider that, as suggested by others,¹⁸⁻²² an increased wall stiffness might have improved ejection fraction by minimizing dyskinesia, as demonstrated by the lower extent of the a-dyskinetic zone in our rt-PA-treated patients (Figure 3). A better global and regional ejection fraction and a reduction in hypokinesia in early rt-PA-treated patients 8 to 10 days from myocardial infarction has also been found in other studies.^{2,3,23,24} The TIMI-1 trial² demonstrated at 8 to 10 days after infarction a reduction in the extent of hypokinesia and an improvement in the kinesis of the infarct zone in patients treated within 7 hours from pain onset. Furthermore, in a subgroup analysis, the same study showed a small but significant increase in ejection fraction in patients who achieved sustained reperfusion. This finding was not observed in patients who had no reperfusion, late reperfusion, or reocclusion.²

In our study 8 to 10 days after AMI, both early and late rt-PA-treated patients had lower end-systolic and end-diastolic volumes with respect to group C patients (Figure 1). This could be the consequence of a reduction in infarct size (lower number of hypokinetic and akinetic-dyskinetic segments) and of an improved left ventricular function due to a better perfusion of the ischemic zone (higher TIMI perfusion grade and patency rate). In fact, early mechanical expansion of the infarcted myocardial segments are, together with the depressed systolic function and impaired diastolic relaxation, the causes of volume overload in AMI.^{25,26} Jeremy et al¹⁷ recently demonstrated that perfusion of the infarct zone during the healing phase is important in preventing continuing infarct expansion and subsequent left ventricular dilation. These findings of smaller ventricular volumes and contained myocardial expansion in patients treated with thrombolytic therapy early in the time course of myocardial infarction are in agreement with other studies.^{4,21,26,27} Furthermore, the analysis of the Italian Group for the Study of Streptokinase in Myocardial Infarction-1 trial, including patients treated within 12 hours from symptom onset with regard to left ventricular volumes and function,²⁷ has shown a con-

tained myocardial expansion and lower ventricular volumes in patients receiving intravenous streptokinase with respect to the control group.

Study limitations: The major limitation of this study was the small number of patients. However, the patients were consecutively considered for entry into the study and, for those admitted between 4 to 8 hours, randomly assigned to receive rt-PA or conventional therapy. Thus, our groups should be general with regard to demographic study. Furthermore, the results are in agreement with experimental data dealing with assessment of postinfarction function and infarct expansion. Because coronary angiography was not performed before rt-PA infusion, we do not know the baseline variables or whether spontaneous thrombolysis had occurred.

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Usefulness of Antithrombotic Therapy in Resting Angina Pectoris or Non-Q-Wave Myocardial Infarction in Preventing Death and Myocardial Infarction (a Pilot Study from the Antithrombotic Therapy in Acute Coronary Syndromes Study Group)

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In a prospective pilot trial of antithrombotic therapy in the acute coronary syndromes (ATACS) of resting and unstable angina pectoris or non-Q-wave myocardial infarction, 3 different antithrombotic regimens in the prevention of recurrent ischemic events were compared for efficacy. Ninety-three patients were randomized to receive aspirin (325 mg/day), or full-dose heparin followed by warfarin, or the combination of aspirin (80 mg/day) plus heparin and then warfarin. Trial antithrombotic therapy was added to standardized antianginal medication and continued for 3 months or until an end point was reached. Analysis, by intention-to-treat, of the 3-month end points, revealed the following: recurrent ischemia occurred in 7 patients (22%) after aspirin, in 6 patients (25%) after heparin and warfarin, and in 16 patients (43%) after aspirin combined with heparin and then warfarin; coronary revascularization occurred in 12 patients (38%) after aspirin, in 12 patients (50%) after heparin and warfarin, and in 22 patients (60%) after aspirin combined with heparin and then warfarin; myocardial infarction occurred in 1 patient (3%) after aspirin, in 3 patients (13%) after heparin and warfarin, and in no patient after aspirin combined with heparin and then warfarin; no deaths occurred after aspirin or after aspirin combined with heparin and then warfarin, but 1 patient (4%) died after warfarin alone; major bleeding occurred in 3 patients (9%) after aspirin, in 2 patients (8%) after heparin and warfarin, and in 3 patients (8%) after aspirin combined with heparin and then warfarin.

Recurrent myocardial ischemia occurred at 3 ± 3 days after randomization. In those who had coronary angioplasty or bypass surgery, revascularization was performed at 6 ± 4 days. During trial therapy, no patient died, had a Q-wave myocardial infarction or a major bleed. Most bleeding complications consisted of blood transfusions during or immediately after bypass surgery. Only 25% of patients enrolled were discharged on trial therapy because of revascularization and withdrawals. Thus, irrespective of the antithrombotic regimen used, and even with aggressive combination therapy, a substantial fraction of patients with unstable angina or non-Q-wave myocardial infarction have recurrent myocardial ischemia and are referred for coronary revascularization. Antithrombotic therapy, coupled with early intervention after recurring ischemia, was associated with a low rate of death or myocardial infarction within the first 3 months.

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The beneficial role of antithrombotic therapy with either antiplatelet agents¹⁻⁴ or anticoagulants^{3,5-8} in patients with unstable angina pectoris has been established. Theroux et al³ compared combination antithrombotic therapy with aspirin plus heparin versus placebo in unstable angina. By design, trial therapy was continued for only 5 to 6 days, and several patients had rebound myocardial ischemic pain after heparin was stopped.⁹ Based upon (1) pathoanatomic observations implicating plaque rupture and thrombosis,¹⁰⁻¹³ (2) limitations in the aforementioned trials, and (3) the potential for a lower medical failure rate with the use of a more aggressive antithrombotic regimen, we studied the efficacy of aspirin combined with anticoagulant therapy in patients with unstable angina or non-Q-wave infarction, or both, administered over a 3-month trial period. This study assessed whether aspirin combined with anticoagulant therapy was superior to either agent alone in reducing the frequency of recurrent myocardial ischemia and the need for coronary angioplasty or bypass surgery.

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TABLE I Screening Process for Patient Selection: First Six Months

Screening Categories	No.	Subgroup No.
Screened (all patients with unstable angina or "rule-out MI")	300	
Met inclusion criteria (rest angina or non-Q-wave infarction)	118	
Excluded	77	
In protocol already		2
Left bundle branch block		5
Coronary bypass surgery within 1 year		10
Coronary angioplasty within 6 months		4
Q-wave MI within 6 weeks		2
Tachyarrhythmia		4
Hypertension		6
Heart failure		8
Peptic ulcer or previous CVA		5
Bleeding tendency		3
Allergy to trial therapy		1
Anemia		5
Other serious illness		14
Need anticoagulants		4
Need chronic aspirin or steroids		4
Eligible	41	
Private physician refused		6
Patient refused		8
Randomized	27 (66% of those eligible)	

CVA = cerebrovascular accident; MI = myocardial infarction; No. = number of patients.

METHODS

Patient selection: The study was conducted at Mount Sinai Hospital and Beth Israel Hospital after approval by the respective institutional review boards concerned with human research. From March 20, 1987, to March 14, 1989, all patients with cardiac pain, resting pain, or non-Q-wave infarction were screened. Men and women between the ages of 21 and 75 years were eligible if they met both of the following inclusion criteria.

First, they must have presented to the hospital with ischemic pain caused by either unstable angina or non-Q-wave infarction defined as follows: (1) recent onset (<4 weeks) of prolonged (≥ 10 minutes) or recurrent (≥ 2 episodes/day) chest pain suggestive of acute myocardial ischemia; (2) pain occurred at rest or with minimal effort, and with no provoking factors; and (3) the last episode of pain occurred within 48 hours of screening.

Second, there must have been definite evidence of underlying ischemic heart disease, as shown by ≥ 1 of the following: (1) transient electrocardiographic changes during chest pain (T-wave changes or ≥ 1 -mm ST-segment deviation) or (2) prior history of myocardial infarction, positive exercise test results or coronary arteriogram, or typical exertional chest pain relieved by rest or nitroglycerin, or both.

Exclusion criteria consisted of the following: evolving Q-wave myocardial infarction, left bundle branch block, angina precipitated by obvious provoking factors (e.g., heart failure, tachyarrhythmia, hypertension [systolic ≥ 160 mm Hg, diastolic ≥ 100 mm Hg]), current use of

or contraindications to anticoagulation, coronary angioplasty within 6 months or coronary bypass surgery within 1 year, or patient unable or unwilling to give consent. Patients with occasional aspirin use were not excluded from this trial. Data obtained during screening in the first 6 months of the trial were recorded (Table I). Fifty-four percent of patients eligible for the study were randomized.

Study protocol: After consent was obtained, patients were randomized to 1 of 3 therapies:

ASPIRIN ALONE: Upon randomization, aspirin 325 mg orally was followed by aspirin 325 mg/day.

HEPARIN FOLLOWED BY WARFARIN ALONE: An intravenous loading dose of heparin 100 U/kg bolus was followed by a continuous infusion to maintain the activated partial thromboplastin time at $2.0 \times$ control for 3 to 4 days. If coronary arteriography did not appear imminent because of recurring pain by the third day, warfarin was started and titrated to maintain the prothrombin time at 1.5 to $2.0 \times$ control (international normalized ratio at 3.0 to 4.5), and heparin was discontinued.

ASPIRIN, PLUS HEPARIN AND THEN WARFARIN: Aspirin 325 mg orally and a bolus of intravenous heparin 100 U/kg were followed by aspirin 80 mg/day, plus a continuous heparin infusion, as in limb 2. By the third day, warfarin was started and titrated, as in limb 2, and heparin was discontinued. Aspirin, 80/mg, was continued along with warfarin. By design, every effort was made to continue the trial therapy for 12 weeks, unless an end point or a withdrawal criterion was reached (see below). After 12 weeks, the decision to continue administration of aspirin or warfarin was made by the private physician.

In addition to the trial therapy, all patients received standard antianginal medical therapy with oral nitrates plus β blockers or calcium antagonists, or both. If pain recurred on this regimen, intravenous nitroglycerin was administered. The dosages of the 3 antianginal drugs were maximized within 48 hours of admission to reduce the systolic blood pressure to ≤ 120 to 130 mm Hg, and to reduce the heart rate to ≤ 65 beats/min. Aspirin containing medication other than that used in the trial drugs was prohibited.

Trial therapy was ended by design for the following reasons: (1) an end point occurred (recurrent ischemia, myocardial infarction, death or bleeding); (2) the patient was found to have normal or nonobstructive coronary artery disease, or a negative exercise tolerance test; (3) coronary revascularization or angioplasty was performed; and (4) noncompliance with medication. Patients who needed revascularization were continued on trial medications until the day of the procedure.

Study end points: There were 3 primary end points:

RECURRENT MYOCARDIAL ISCHEMIA: This was defined as the presence of recurrent angina at rest with ischemic electrocardiographic changes occurring despite full medical therapy. Full medical therapy was defined as receiving a minimum of 2 antianginal medications, resulting in a baseline resting heart rate of ≤ 65 beats/min and a systolic pressure ≤ 120 to 130 mm Hg.

TABLE II Clinical Characteristics of the Study Population

Demographics	Aspirin n = 32 (%)	Heparin/ Warfarin n = 24 (%)	Aspirin + Hep/Warf n = 37 (%)	Total Group n = 93 (%)
Age (mean yrs)	62	61	63	62
Male gender	18 (56)	16 (68)	22 (59)	56 (60)
Previous angina or MI	24 (75)	22 (92)	30 (81)	76 (82)
Interval from onset of angina or first MI (mos.)	35	72	40	47
Cigarette smoker	15 (47)	14 (58)	22 (59)	51 (55)
Systemic hypertension	17 (53)	11 (46)	18 (49)	46 (49)
Diabetes mellitus	11 (34)	8 (33)	15 (41)	34 (37)
Medication before admission				
Nitrates	13 (41)	12 (50)	19 (51)	44 (47)
β blockers	8 (25)	8 (33)	7 (19)	23 (25)
Calcium antagonists	12 (37)	12 (50)	17 (46)	41 (44)
Recent aspirin	8 (25)	7 (29)	14 (38)	29 (31)
In-Hospital Data				
Time between randomization and last resting pain (hours)	14	11	12	12
ST-T changes at randomization	22 (69)	17 (71)	28 (76)	67 (72)
Present with non-Q infarct (%)	11 (34)	11 (46)	13 (35)	34 (37)
Treatment during hospitalization				
Nitrates	28 (88)	21 (88)	30 (81)	79 (85)
β blockers	12 (37)	11 (46)	13 (35)	36 (39)
Calcium antagonists	27 (84)	22 (92)	29 (78)	78 (84)
Coronary Arteriography	18 (56)	15 (63)	25 (65)	58 (62)
Percentage* with diseased vessels (>70%)				
0	2 (11)	2 (13)	2 (8)	6 (10)
1	4 (22)	2 (13)	6 (24)	12 (21)
3	5 (28)	4 (27)	4 (16)	13 (22)
3	6 (33)	6 (40)	11 (44)	23 (40)
Left main artery	1 (6)	1 (7)	2 (8)	4 (7)
PTCA	7 (22)	4 (17)	9 (24)	20 (22)
CABG	5 (16)	8 (33)	13 (35)	26 (28)
Non-obs CAD or neg ETT	8 (25)	3 (12)	4 (11)	15 (16)
Duration on trial therapy (days)	29	16	8	17

* Percentage of those 58 patients who underwent arteriography. All other percentages are percentages of the total population (n = 93).
 CABG = coronary artery bypass grafting; Hep/Warf = heparin followed by warfarin; neg ETT = negative maximal exercise tolerance test; Non-obs CAD = nonobstructive coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table I.

MYOCARDIAL INFARCTION: This was defined as chest pain associated with new and persistent ST-T-wave changes or Q waves, accompanied either by a rise in serum creatine kinase to >2 times the upper limit of normal or by an increase of $\geq 50\%$ in creatine kinase activity above the preceding sample but at least 1.5 times the upper limit of normal. Perioperative myocardial infarction was identified by a combination of electrocardiographic criteria and enzyme criteria. However, in this setting, the creatine kinase MB isoenzyme must be $>50 \mu\text{ml}$ (normal is $<16 \mu\text{ml}$). Only those infarctions considered as events clearly separate from the initial cardiac event that qualified the patient for randomization were considered as end points.

TOTAL DEATHS: All deaths, regardless of etiology, were end points. A death occurring <30 days after coronary angioplasty or bypass surgery was considered a perioperative death.

There were 3 secondary end points: (1) recurrent chest pain with or without acute electrocardiographic changes; (2) revascularization with coronary angioplasty or bypass surgery; and (3) major bleeding, which was defined as bleeding requiring a transfusion of ≥ 2 units of blood, or corrective surgery, or both, or as

bleeding that resulted in death, disability, intracranial or retroperitoneal hemorrhage. After coronary bypass surgery, a transfusion of >2 units of blood was considered a major bleed.

Follow-up and protocol deviations: Trial therapy and study end points were monitored daily during the hospital stay. After discharge, patients were reevaluated at 6 and 12 weeks using the interval history, any readmission hospital records, 12-lead electrocardiogram, hematocrit, stool for occult blood, and prothrombin time. Trial therapy was initiated in ≤ 3 hours of randomization in all patients. One patient was not included in this analysis; she signed out against medical advice before trial therapy was begun. Protocol deviations occurred in 17 patients; their follow-up, however, is included in the analysis: 2 patients were inappropriately randomized; 2 were noncompliant and stopped their trial therapy prematurely; and private physicians referred 13 patients for revascularization despite their being asymptomatic on trial therapy. Trial therapy was continued until the time of their revascularizations.

In-hospital follow-up was complete. After hospital discharge, 5 patients were lost to follow-up, and no determination could be made regarding their vital or clinical

TABLE III End Points

	Aspirin n = 32 (%)	Heparin/ Warfarin n = 24 (%)	Aspirin + Hep/Warf n = 37 (%)	Total Group n = 93 (%)
Primary end points				
Recurrent ischemia (pain + ECG)	7 (22)	6 (25)	16 (43)	29 (31)
MI (total)	1 (3)	3 (13)	0	4 (4)
Perioperative infarction	0	2 (8)	0	2 (2)
Death (total)	0	1 (4)	0	1 (1)
Death off trial therapy	0	1 (4)	0	1 (1)
Secondary end points				
Recurrent chest pain	16 (50)	10 (42)	23 (62)	49 (52)
PTCA or CABG	12 (38)	12 (50)	22 (60)	48 (50)

Pain + ECG = chest pain accompanied by electrocardiographic changes; other abbreviations as in Tables I and II.

cal status by the end of the 12-week trial period. Two of these patients were in the aspirin-alone group, and 3 were in the heparin-alone group.

Characteristics of the study population: Clinical characteristics, including baseline demographics as well as data acquired after randomization, are listed in Table II. The study population (n = 93) consisted of a group that was at high risk for coronary artery disease. More than two-thirds of the study group had ≥ 1 coronary risk factor before admission, and 82% had either a previous myocardial infarction or a history of stable angina. In 18% of patients, the qualifying episode of resting pain was their first manifestation of coronary disease. Sixty-seven percent of the patients recalled having had an earlier episode of resting pain within the 4 weeks before the qualifying episode of resting pain. Trial therapy was initiated at a mean of 12 ± 10 hours after the last episode of resting pain. Patients were distributed among the 3 treatment groups as follows: aspirin alone—32 patients; heparin and warfarin alone—24 patients; and aspirin plus heparin and then warfarin—37 patients. At randomization, 72% of the study group had ischemic electrocardiographic changes.

Statistical analysis: Continuous variables are presented as mean \pm standard deviation. Multiple comparisons among the 3 treatment groups were not undertaken because of the relatively small sample size. The 5 patients who were lost to follow-up after hospital discharge were distributed among the 3 treatment groups and were counted as having experienced no end points during the 3-month follow-up.

RESULTS

Primary end points: RECURRENT MYOCARDIAL ISCHEMIA, INFARCTION, OR DEATH: Despite maximal antianginal therapy, recurrent myocardial ischemia (chest pain and electrocardiographic changes) occurred in 29 patients, 31% of the total population (Table III). Although the frequency of this event ranged from 22% in the aspirin-alone group to 43% in the aspirin-plus-heparin group, application of the chi-square statistic revealed no significant differences among the 3 treatment groups in this end point. Recurrent myocardial ischemia occurred at a mean of 3 ± 2 days after initiation of trial therapy. Two patients developed myocardial infarction while on

TABLE IV Complications

	Aspirin n = 32 (%)	Heparin/ Warfarin n = 24 (%)	Aspirin + Hep/Warf n = 37 (%)	Total Group n = 93 (%)
On trial therapy				
Major bleeding (total)	0	0	0	0
Minor bleeding (total)	1 (3)	0	1 (3)	2 (2)
Hematuria + stool guaiac	1	0	0	1
Off trial therapy (related to PTCA or CABG)				
Major bleeding (total)	3 (9)	2 (8)	3 (8)	8 (9)
Wound bleed and transfusion	3	0	2	5
Requiring surgical repair	0	2	0	2
GI bleed and transfusion	0	0	1	1
Minor bleeding (total)	0	1 (4)	0	1 (1)
Related to CABG	0	1	0	1

GI = gastrointestinal; other abbreviations as in Table II.

trial antithrombotic therapy and before any revascularization procedure. In both cases they were non-Q-wave infarctions. Two additional patients developed myocardial infarction during coronary bypass surgery and both were in the heparin- and warfarin-alone group. During the trial therapy, there were no deaths. However, after hospital discharge, there was 1 fatality: a noncompliant patient who had stopped her trial medication prematurely (warfarin alone) experienced sudden death 2 weeks after discharge.

Secondary end points: RECURRENT CHEST PAIN AND REVASCULARIZATION: Recurrent chest pain (with or without electrocardiographic changes) occurred in 49 patients, 52% of the total population at a mean of 3 ± 3 days after initiation of the trial therapy (Table III). At the time of recurrent pain, 86% of these 49 patients were on a minimum of 2 antianginal drugs, including intravenous nitroglycerin. No significant difference in the incidence of recurrent pain was observed among the 3 treatment groups. In the 49 patients with recurrent pain, revascularization by either coronary angioplasty or coronary bypass surgery was undertaken in 67%, whereas, in the 44 patients without recurrent pain, 13 (29%) underwent revascularization. Ten of the 13 patients without recurrent pain, who were revascularized, had severe multivessel disease. For the population as a whole (n = 93), the mean duration from randomization to diagnostic catheterization was 4 ± 3 days, and the mean duration from randomization to revascularization was 6 ± 4 days. Forty-one of the 46 patients who underwent revascularization were operated on during the initial hospitalization and the remaining 5 were revascularized during the first 3 months after discharge. A total of 15 patients (16%) had either nonobstructive coronary artery disease or negative maximal stress test results, and their trial therapy was discontinued. Only 25 of the original 93 patients (26%) were discharged on trial therapy.

MAJOR BLEEDING COMPLICATIONS: There were no episodes of spontaneous major bleeding during the trial therapy in any of the 3 groups (Table IV). Two patients experienced minor bleeding during the trial therapy, ne-

cessitating withdrawal of therapy in 1 patient. No major bleeding occurred as a result of diagnostic cardiac catheterization. Off of trial therapy, 8 patients experienced major bleeding, all of which was related to revascularization. One patient required surgical repair of the femoral artery puncture site after coronary angioplasty. The remaining 7 patients experienced major bleeding in relation to coronary bypass surgery: 5 of the 7 required >2 units of blood transfusion for perioperative blood loss, 1 underwent reoperation for a slipped ligature, and another had a perioperative gastrointestinal bleed. Patients in the aspirin plus heparin and then warfarin group did not experience a greater frequency of either spontaneous bleeding or perioperative bleeding. During the same time period, 49% of *all* patients undergoing coronary bypass surgery at this hospital required blood transfusion. The average blood requirement for these patients was 2.3 units. In contrast, of the 27 patients who underwent bypass surgery in our study, only 7 (26%) required blood, and their average requirement was 2.8 units.

DISCUSSION

Unstable angina pectoris represents a broad spectrum, ranging from progressive or accelerating angina to the higher risk subset of resting angina with reversible electrocardiographic changes.¹⁴ Previous placebo-controlled therapeutic trials established a beneficial role for antithrombotic therapy with aspirin alone or with heparin or warfarin alone in progressive or accelerating angina.^{1,2,4,7} With regard to the higher risk patients with resting unstable angina pectoris or non-Q-wave myocardial infarction, several trials of antithrombotic therapy have been reported^{3,6,8} but the trial therapy was limited only to the first week after presentation.^{6,8} Theroux et al,³ for example, compared antithrombotic therapy with either aspirin or heparin, or both, versus placebo, in the high-risk subset of patients presenting with pain either at rest or with minimal effort and with electrocardiographic changes. They observed that, in this high-risk subset, as well, antithrombotic therapy was more effective than placebo was in reducing the rate of myocardial infarction or death. Furthermore, only heparin, or the combination of aspirin plus heparin, significantly reduced the rate of refractory angina. However, by design, all patients in this study³ were referred for catheterization and the trial therapy was ended 5 to 6 days after randomization. Subsequently, several patients experienced rebound myocardial ischemic pain after heparin was stopped,⁹ and, at 3-month follow-up, 48% of the original study population underwent coronary revascularization.³ More recently, Neri Serneri et al⁸ compared different antithrombotic regimens in a small group of patients with refractory angina. They observed a significant reduction in episodes of silent ischemia in patients randomized to a continuous heparin infusion but not in patients randomized to aspirin or to the thrombolytic agent tissue plasminogen activator.⁸

Despite these trials, several questions remain: (1) Is there an effective "medical" regimen for this acute coronary syndrome that can substantially reduce the incidence of recurrent myocardial ischemia and thereby

minimize the need for invasive diagnostic catheterization and revascularization procedures? (2) In view of the dynamic intraarterial processes precipitating the acute coronary syndromes, does more aggressive antithrombotic therapy with platelet inhibition *plus* anticoagulation offer more benefit than either agent alone? (3) Is one antithrombotic regimen better at reducing perioperative complications in patients presenting with unstable angina? Our study was designed to enroll high-risk patients with either resting angina or non-Q-wave infarction and to continue medical therapy (antianginal plus trial antithrombotic therapy) for 3 months after presentation. In addition, our analysis included events occurring during or after crossover to revascularization, and provided pilot data on the relative efficacy and safety of combination antithrombotic therapy administered over a 3-month trial period. Several findings emerged.

We observed a disappointingly high rate of recurrent chest pain prompting catheterization and revascularization in all 3 treatment groups. Specifically, aggressive combination therapy did not reduce the frequency of recurrent pain and of subsequent coronary angioplasty or coronary bypass surgery, compared to that seen with single antithrombotic therapy. In all, between the 51% of patients withdrawing from trial therapy because of revascularization, and the 16% of patients with nonobstructive coronary disease or negative stress test results, only 26% of the original cohort were discharged on the trial therapy and even fewer reached the 3-month follow-up on therapy. Despite our intention to attempt to continue antithrombotic therapy for 3 months, our rate of failure of medical therapy—that is, need for revascularization—was similar to that of Theroux,³ Neri Serneri⁸ and their co-workers—about 50%. Of interest, Ouyang et al,¹⁵ in 1984, observed a similar rate of medical failure and revascularization, about 40 to 50%, with maximal antianginal therapy. Therefore, while the addition of conventional antithrombotic therapy to antianginal medication has had a beneficial impact on the rate of death and myocardial infarction,¹⁻⁷ it has not altered the natural history of resting unstable angina or non-Q-wave infarction in the face of the need for definitive revascularization.

Revascularization in the setting of unstable angina is associated with a higher complication rate.¹⁶⁻¹⁹ Our study is the first to analyze perioperative ischemic events and bleeding prospectively in patients with unstable angina undergoing revascularization while on different antithrombotic regimens. Specifically, 2 of the 3 infarctions in our heparin- or warfarin-alone group occurred during coronary bypass surgery. In contrast, none of the patients treated with aspirin experienced a perioperative infarction, or died. Earlier investigators have already noted the beneficial effect of aspirin given before revascularization.^{20,21}

The combination of aspirin plus heparin and then warfarin was associated with the lowest rate of infarction or death, although the relatively small sample size of our study groups must be kept in mind. The preliminary report of Wallentin and the RISK study group⁴ is the first study with enough power to observe a statistically significant benefit of combination therapy over

placebo and over short-term heparin-alone therapy. It might be anticipated that the routine use of antithrombotics, especially the combination of aspirin with anticoagulants, would produce more adverse effects than either aspirin or heparin alone. In fact, we did not observe any spontaneous major bleeding during the trial therapy or major bleeding related to diagnostic catheterization. The lower rate of bleeding observed in the present study, compared to that observed by Theroux et al,³ could be explained in two ways. They accepted a decrease in hematocrit levels alone as a criterion for a "serious bleed," and they used a dose of 650 mg/day of aspirin. In the present study, 325 mg was used in the aspirin-alone limb, and 80 mg in the combination limb. In addition, the combination of low-dose aspirin plus heparin and then warfarin did not result in an increased rate of blood transfusion during coronary bypass surgery.

Study limitations: First, patients were prospectively enrolled and randomized, but the trial therapy was not blinded. However, the main end points were identified by daily interviews of the patients, and by review of the daily progress notes in the chart and of serial cardiac enzymes. These daily notes were written by the patients' personal physicians and by nurses who were unaware of the general progress of the study and the emerging trends. Second, different dosages of aspirin were used in the 2 aspirin-containing limbs. In parallel with the study of Lewis et al,¹ we used 325 mg/day in the aspirin-alone limb, as the standard. For the combination limb, a dose of 80 mg of aspirin was chosen because this low dose would minimize aspirin-related adverse effects, which are dose-dependent. Third, our patient population was relatively small. In our ongoing trial, we are evaluating only 2 limbs, aspirin versus aspirin plus heparin and then warfarin, and will aim to enroll several hundred patients to achieve an adequate power to detect significant differences in treatment effect.

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Angiographic Progression to Total Coronary Occlusion in Hyperlipidemic Patients After Acute Myocardial Infarction

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The progression of coronary artery stenosis to total occlusion was assessed in 413 hyperlipidemic patients with a previous myocardial infarction. Coronary angiograms were recorded at baseline, 3 (n = 312), and 5 years (n = 248) after initial study and analyzed by 2 independent readers. There were 177 (43%) patients with 1-, 130 (31%) with 2-, and 61 (15%) with 3-vessel disease ($\geq 50\%$ diameter narrowing), whereas 45 (11%) did not have significant disease within a major coronary vessel at baseline. A new finding of total occlusion occurred in 4% (30 of 748) and 7% (40 of 605) of major coronary artery segments at 3 and 5 years, respectively. The risk of progression to total occlusion was higher if the initial stenosis was $>60\%$ compared to lesions $\leq 60\%$ both at 3 years (19 of 143 = 13% vs 11 of 605 = 2%; $p < 0.001$) and 5 years (27 of 91 = 30% vs 13 of 514 = 3%; $p < 0.001$). The frequency of occlusion was highest for the right coronary artery by 5 years (18 of 167 = 11% for right vs 8 of 225 = 4% for circumflex vs 14 of 213 = 7% for left anterior descending coronary arteries; $p < 0.02$). Clinical and laboratory data revealed that myocardial infarction was associated with a new total occlusion in 23% of patients (7 of 30) at 3 years and in 64% (25 of 39) at 5 years. Serum cholesterol and triglyceride levels were significantly higher in patients with a new finding of total occlusion at 5 years. This prospective serial angiographic study showed that the extent of initial coronary artery narrowing was significantly associated with the risk of progression to total occlusion. (Am J Cardiol 1990;66:1293-1297)

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It has been suggested that angiographic progression of coronary artery disease is related to both the time between angiograms and the degree of the stenosis seen at initial angiography.¹ However, other studies suggest that angiographically demonstrable progression of coronary artery disease is unpredictable except for very high-grade lesions (98 or 99%) that frequently progress to total occlusion.² Such contradictory results may occur, at least in part, because patients in most retrospective studies had clinical events necessitating early re-catheterization. That method of selection may have produced results not representative of the true natural history of coronary artery disease.

In the current prospective study, as part of the multicenter clinical trial "Program On the Surgical Control of Hyperlipidemia" (POSCH), we qualitatively analyzed serial coronary angiography at 3 and 5 years after initial catheterization to determine the angiographic predictability of the progression of coronary artery disease. We also used univariate analysis to determine whether other risk factors may be useful in predicting the progression of coronary atherosclerosis.

METHODS

The POSCH study is a multicenter, secondary coronary disease interventional program. It was designed to determine the effects of lipid reduction by partial ileal bypass surgery on atherosclerotic cardiovascular disease in a hyperlipidemic population of patients who have survived a first myocardial infarction.³ Criteria for entry into the POSCH study included age 30 to 64 years, a first myocardial infarction within 6 to 60 months of randomization, plasma cholesterol level ≥ 220 mg/dl or 200 to 219 mg/dl with a low-density lipoprotein of ≥ 140 mg/dl after 6 weeks of dietary therapy, diastolic blood pressure of <105 mm Hg, body weight $<40\%$ above the ideal, and the absence of diabetes mellitus, nephrotic syndrome, stroke or transient intracerebral accident, unstable angina or serious chronic cardiac disease.

Patients: A total of 5,469 patients were screened, with 417 patients randomized to the control group and 421 subjects to the surgical group.⁴ The surgical group underwent partial ileal bypass surgery with dietary lipid restriction, whereas the control group received dietary counseling for lipid reduction (Figure 1). All patients underwent follow-up clinical evaluation, including resting and exercise (modified Bruce) electrocardiography

TABLE I Clinical Characteristics at Baseline, Three and Five Years

Variable	Baseline (n = 413)	Three Years (n = 312)	Five Years (n = 248)
Age (yrs)			
Mean	51 ± 8		
<40 (%)	9	8	6
40-49 (%)	32	33	35
50-59 (%)	47	47	45
≥60 (%)	12	13	13
Gender (%)			
M	92	92	92
F	8	8	8
Hx Smoking (%)			
Never	15	12	13
Not cigarettes	5	4	4
Current cigarettes	32	31	31
Past	52	53	52
Angina pectoris (%)			
Yes	46	45	46
No	54	55	54
MI Type (%)			
Q-wave	81	81	81
Non-Q-wave	19	19	19
Cholesterol (mg/dl)			
<250	61	61	64
250-299	31	31	29
>300	8	8	7

Hx = history; MI = myocardial infarction.

TABLE II Serum Lipid Profile at baseline, Three and Five Years

	Baseline (n = 413)	Three Years (n = 311)	Five Years (n = 246)
Triglycerides (mg/dl)	199 ± 140	179 ± 97*	194 ± 117
Cholesterol (mg/dl)	251 ± 35	240 ± 34†	239 ± 32†
HDL	41 ± 10	39 ± 9*	40 ± 10
LDL	179 ± 37	172 ± 36†	167 ± 34†
Ratio (%)			
HDL/LDL	23 ± 7	24 ± 7	25 ± 8*
HDL/cholesterol	16 ± 4	17 ± 4†	17 ± 4*†

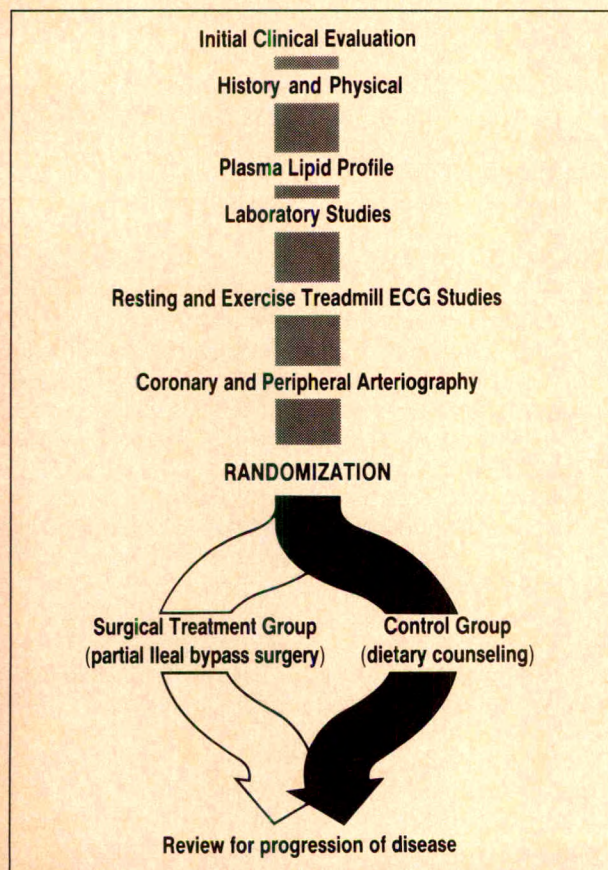
* p < 0.05, † p < 0.001 compared to baseline; † numbers appear identical due to rounding off.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

TABLE III Percent Progression to Total Occlusion as Predicted by Location of Initial Stenoses*

Coronary Artery	Three Years	Five Years
Right	7 (14/208)	11 (18/167)
Left circumflex	3 (7/276)	4 (8/225)
Left anterior descending	3 (9/264)	7 (14/213)
Total	4 (30/748)	7 (40/605)
p Value	0.055	0.017

* Number of arteries with <100% occlusion at baseline.

**FIGURE 1.** Schematic of patient evaluation on admission to the Program On The Surgical Control of Hyperlipidemia protocol. Solid arrow traces the control group, the cohort of patients studied in this report. ECG = electrocardiographic.

at 3 months, 1, 2, 3, 4 and 5 years, with selective coronary arteriography repeated at 3 and 5 years. The current study is limited to patients randomized to the control group—a total of 413 patients with baseline coronary angiograms repeated in 312 and 248 patients at 3 and 5 years, respectively.

Coronary angiographic analysis: All coronary angiograms were reviewed centrally by a panel of 2 cardiologists. The coronary arterial system was divided into 14 segments, with the right coronary artery divided into 4 segments, the posterior descending coronary artery into 2 segments, the left main coronary artery into 2 segments, the left anterior descending coronary artery into 3 segments and the left circumflex artery into 3 segments. Film pairs for any given patient were read by 2 observers blinded to the temporal sequence of films, treatment and patient identity.

Definitions: Coronary artery disease was defined as a ≥50% diameter narrowing in a major coronary artery. Occlusion was defined as total obstruction without antegrade filling in a previously patent segment.

Statistical analysis: Univariate analysis, chi-square and *t* tests were used as appropriate, with *p* < 0.05 considered statistically significant.

RESULTS

Table I lists the clinical characteristics on entry for all patients enrolled in this study at baseline, 3, and 5 years. At baseline there were 177 patients (43%) with 1-, 130 patients (31%) with 2-, and 61 patients (15%) with 3-vessel disease, whereas 45 patients (11%) did not have disease in a major coronary vessel. The ejection fraction was $56 \pm 12\%$ at baseline. From baseline to 3 years, 101 patients were removed from the study (16 patients died; baseline film was lost for 14; follow-up

TABLE IV Progression to Occlusion by Severity of Initial Lesion (Percentage)

Initial Stenosis (%)	Coronary Artery					
	Left Anterior Descending		Left Circumflex		Right	
	Three Years	Five Years	Three Years	Five Years	Three Years	Five Years
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
0	51 (2)	60 (0)	109 (0)	89 (1)	27 (0)	27 (0)
1-20	46 (0)	29 (0)	46 (0)	44 (0)	40 (3)	34 (6)
21-40	95 (1)	73 (1)	66 (0)	45 (0)	49 (4)	42 (12)
41-60	29 (7)	25 (4)	26 (12)	26 (8)	21 (5)	20 (5)
61-75	14 (0)	4 (25)	7 (0)	8 (13)	13 (8)	10 (20)
76-90	19 (11)	11 (46)	8 (13)	8 (25)	37 (16)	19 (26)
91-95	4 (25)	6 (50)	12 (17)	1 (0)	15 (13)	10 (20)
96-99	6 (33)	5 (60)	2 (50)	4 (50)	6 (17)	5 (20)

film was lost for 2; the follow-up film was not done for 25; the 3-year follow-up visit was missed by 23; and 21 patients underwent revascularization before 3-year evaluation). From baseline to 5 years, 169 patients were removed from the study (31 patients died; baseline film was lost for 13; 5-year film was lost for 1; the follow-up procedure was not done for 42; the 5-year follow-up visit was missed by 25 patients; and 53 patients underwent revascularization before the 5-year evaluation). The study population had, cumulatively, 32 deaths (1 patient died after early 5-year angiography), 81 coronary artery bypass graft surgeries, and 9 percutaneous transluminal coronary angioplasties. Repeat analysis of the baseline clinical characteristics at 3 and 5 years showed that measured characteristics of the patient population did not significantly change during the study (Table I). Serum triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein, high-density/low-density lipoprotein and high-density lipoprotein/cholesterol ratios measured at baseline, 3, and 5 years are listed in Table II. Patients who required revascularization before the next coronary angiogram were included in the analysis but repeat analysis with exclusion of these patients did not significantly alter the findings of the study.

After 3 years of follow-up, excluding 188 preexisting total occlusions, 30 of 748 (4%) segments in the 3 major coronary arteries progressed to total occlusion, whereas 40 of 605 (7%) segments became totally occluded at 5 years. When progression to total occlusion was com-

pared for the 3 major arteries, the right coronary artery had a significantly higher risk ($p < 0.02$) than either the left anterior descending coronary artery or left circumflex artery at 5 years (Table III).

The risk of progression to total occlusion increased proportionally to severity of initial stenosis (Table IV). Vessels with minimal diameter narrowing rarely became totally occluded (0 to 2%) even at 5 years, whereas the risk of finding a new total occlusion increased significantly (17 to 60%) if the initial diameter narrowing was $\geq 95\%$. The risk of progression to total occlusion was significantly higher if the initial stenosis was $>60\%$ ($p < 0.001$). The frequency of progression to total occlusion was highest in the left anterior descending coronary artery by 5 years, if the initial stenosis was $>60\%$, but this distribution failed to reach statistical significance ($p = 0.09$; Table V).

Among measured characteristics, including age, gender, smoking history, family history of cardiac disease,

TABLE V Percent Progression to Total Occlusion as Predicted by Severity of Initial Stenoses (No./Total Lesions)

Coronary Artery	Three Years		Five Years	
	$\leq 60\%$	$> 60\%$	$\leq 60\%$	$> 60\%$
Right	3 (4/137)	14 (10/71)	7 (8/123)	23 (10/44)
Left circumflex	1 (3/247)	14 (4/29)	2 (3/204)	24 (5/21)
Left anterior descending	2 (4/221)	12 (5/43)	1 (2/187)	46 (12/26)
Total	2 (11/605)	13 (19/143)*	3 (13/514)	30 (27/91)*

* $p < 0.001$ when $\leq 60\%$ is compared to $> 60\%$.**TABLE VI** Prediction of Progression to Total Occlusion Serum Lipid Profile

Lipid (mg/dl)	Did Not Progress (n = 281)	Progress to Occlusion (n = 30)	p Value
Three Years			
Triglycerides	175 \pm 91	209 \pm 140	0.068
Cholesterol	240 \pm 34	238 \pm 36	0.793
HDL	39 \pm 9	40 \pm 9	0.605
LDL	173 \pm 36	160 \pm 39	0.067
Ratio (%)			
HDL/LDL	24 \pm 7	26 \pm 8	0.055
HDL/cholesterol	17 \pm 4	17 \pm 5	0.393
Five Years			
	(n = 201)	(n = 35)	
Triglycerides	183 \pm 92	254 \pm 210	0.001
Cholesterol	236 \pm 30	252 \pm 38	0.008
HDL	40 \pm 9	40 \pm 11	0.662
LDL	168 \pm 32	169 \pm 44	0.678
Ratio (%)			
HDL/LDL	25 \pm 7	25 \pm 11	0.835
HDL/cholesterol	17 \pm 4	16 \pm 6	0.216

Values for p were calculated as paired changes from baseline. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

TABLE VII Comparison of Coronary Artery Disease Progression Studies

Investigators	Year	No.	Interval Progress		Pre	Time
			(mos)	%		
Bruschke et al ¹	1981	256	1-?	1 to 20	+	+
Shub et al ²	1981	65	24	22	0	0
Kramer et al ⁵	1983	317	30	49	+	+
Gensini and Kelly ⁶	1972	120	36	75 c CAD	+	+
				5 s CAD		
Bruschke et al ⁷	1989	168	40	39/41	+	0
Moise et al ⁸	1984	313	38	44	+	+
Bemis et al ⁹	1973	72	24	52	0	0
Marchandise et al ¹⁰	1978	48	42	0 s CAD	+	?
				27 c CAD	+	+
Rosch et al ¹¹	1976	58	26	33	—	—
Visser et al ¹²	1986	300	30	56	+	—
Ishikawa et al ¹³	1986	227	36	32	+	—
Nash et al ¹⁴	1977	119	21	89	—	—
Singh ¹⁵	1984	52	50	33	0	—
Halon et al ¹⁶	1985	26	29	12	—	—
Kroncke et al ¹⁷	1988	119 Med	60	36	+	—
		109 Sur	60	38	+	—
This study	1990	417	36/60	4/7*	+	+

* Progression to total occlusion.

c = with; CAD = coronary artery disease; Interval = time between studies; Med = medical treatment; Pre = predictability of progression based on initial degree of stenosis; s = without; Sur = surgical treatment; Time = progression of disease as time dependent; + = present; 0 = absent; ? = not determinable; — = data not given.

blood pressure, heart rate, exercise test duration, fasting blood glucose, serum triglycerides and cholesterol levels, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein/low-density lipoprotein/cholesterol ratio and high-density lipoprotein/cholesterol ratio, only serum triglyceride and total cholesterol levels demonstrated an association with the progression to total occlusion by 5 years (Table VI). Of all new total occlusions, 23% (7 of 30) were associated with clinical evidence of myocardial infarction by 3 years and 64% (25 of 39) by 5 years.

DISCUSSION

The value of initial angiography in predicting the progression of coronary disease remains controversial,^{1,2} with possible bias in patient selection⁵ producing conflicting conclusions. A review of 15 published studies (Table VII)^{1,2,5-17} revealed that most data were obtained retrospectively from symptomatic patients requiring recatheterization. Twelve to 89% of coronary arteries demonstrated further progression on repeat catheterization, when restudied at 21 to 60 months. In 9 of the 15 studies,^{5-8,10-13,17} the investigators reported the progression of coronary artery disease predictable by initial angiography but in only 4 studies did the investigators report data on progression to total occlusion. Moise et al⁸ demonstrated a 31% risk of new occlusion if the initial stenosis was $\geq 90\%$. Singh¹⁵ reported similar results of 30%, whereas Halon et al¹⁶ showed an overall risk of 3% for occlusion at 26 months, with risk increasing to 24% if the initial stenosis was $\geq 75\%$. Moreover, Kramer et al⁵ showed that only 6% of segments with 1 to 30% stenosis developed total occlusion at 5 years versus 33% of patients with initial lesions of 91 to 99%.

Retrospective study in a small number of patients has shown that significant progression of disease correlates with the presence of hyperlipidemia.⁹ The current study also showed that patients with progression to total occlusion appeared to have higher serum cholesterol and triglyceride levels at 5 years. In the current study, lesions of the right coronary artery were most likely to progress to total occlusion by 5 years. This is consistent with observations reported in another prospective trial.¹⁷

In this study all paired angiograms were reviewed by 2 angiographers with consensus reading and a coding system that divided coronary arteries into 14 small segments. Although there may have been some degree of disagreement as to the relative extent of stenosis within a given vessel, a new finding of total occlusion is less subjective. It has been shown that visual interpretation, which has been used in most progression studies, tends to underestimate the severity of coronary occlusions found at autopsy.¹⁸ Quantitative angiography using computer-assisted methods appears to be more accurate than consensus interpretation¹⁹ because the latter is subject to interobserver variability and to the experience of the panel members. Nonetheless, good agreement can be reached using consensus panel interpretation,²⁰ which is relatively reliable in the assessment of the progression of coronary disease.¹⁷ Our findings suggest that the risk of progression to total occlusion is increased in proportion to the degree of initial stenosis assessed by consensus interpretation. The risk of occlusion was also significantly higher if the original stenosis was $>60\%$. These data obtained by prospective angiography appeared to confirm previous retrospective observations. Our study also illustrates that progression to total occlusion is not necessarily associated with clinical evidence of myocardial infarction. It is possible that sufficient collateral circulation may have developed preceding progression to total occlusion and thus prevented the occurrence of infarction.

This study demonstrated that coronary angiography provides valuable information concerning the risk of progression to total occlusion. Early angiography may be important in selecting patients with high potential for progression to complete obstruction. Because the lipid profile of the population and because patients with other risk factors such as diabetes mellitus and essential hypertension have been excluded, our conclusions should be restricted to the current study population and extended to other populations with caution.

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APPENDIX

THE POSCH GROUP

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The Western Washington Myocardial Infarction Registry and Emergency Department Tissue Plasminogen Activator Treatment Trial

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This study comprised a registry and an emergency department treatment trial using recombinant tissue plasminogen activator. During 1 year, 1,028 patients with documented acute myocardial infarction (AMI) were evaluated for eligibility for thrombolytic therapy. Of these, 221 patients (22%) were eligible for thrombolytic therapy under currently accepted criteria, 175 (79%) of them were correctly identified by emergency department physicians for thrombolytic therapy, and 160 were enrolled in the trial. Only 3 patients (2%) enrolled by emergency department physicians did not subsequently evolve documented AMI. In all, 807 patients (78%) were ineligible for thrombolytic therapy: 335 (33%) because of ≥ 1 contraindications, 364 (36%) because of nondiagnostic electrocardiograms on presentation, and 105 (10%) because of age >75 years, or >6 hours of chest pain at presentation, or both. Mortality in treated patients at 14 days was 5.6%, and survival at 1 year was 92%. The mean time from hospital arrival to thrombolytic treatment was 55 ± 27 minutes. Initial management of AMI with recombinant tissue plasminogen activator in the emergency department provided rapid and safe treatment comparable to that reported in trials that started treatment in the coronary care unit. The proportions of eligible patients could be increased from 1 in 5 to 1 in 3, if patients currently excluded only because of age >75 years or because of >6 hours of chest pain were offered treatment.

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The treatment of acute myocardial infarction (AMI) with thrombolytic agents has been shown to restore blood flow in the infarct-related artery,¹ improve ventricular function,² decrease infarct size³ and reduce mortality.⁴⁻¹⁰ Because maximal benefits occur with early therapy, rapid and efficient actions in identifying eligible patients and initiating treatment are desirable.¹¹ Making the diagnosis and starting treatment of AMI in the emergency department can reduce the delay to initiation of thrombolysis.¹² We evaluate the efficacy, safety and practicality of having emergency department physicians administer intravenous recombinant tissue plasminogen activator (rt-PA) to patients with AMI in hospital emergency departments. We also evaluate the proportion of all patients with AMI who were eligible for thrombolytic therapy and the reasons for ineligibility.

METHODS

Myocardial Infarction Registry: Between January 15, 1987, and January 15, 1988, all patients with documented AMI as a primary or secondary diagnosis (International Classification of Diseases codes 410.0 to 413.9) at 8 hospitals in the Seattle-Tacoma, Washington, metropolitan area were identified. From the medical record, the study nurse recorded patient age and gender, presence or absence of inclusion and exclusion criteria for the rt-PA study, reason the patient (if eligible) was not enrolled in the study, initial and highest blood pressure during the first hour in the hospital and the electrocardiographically determined infarct location. The nurse also recorded the time of chest pain onset, mode of arrival to the hospital, time of arrival of ambulance or paramedics (if used) and the time of arrival in the emergency department, as well as the use of other thrombolytic agents, cardiac catheterization, coronary angioplasty and coronary artery bypass grafting. Finally, we obtained the vital status at the time of hospital discharge.

Recombinant tissue plasminogen activator treatment trial: **PATIENT ENROLLMENT:** All patients presenting to emergency departments in participating hospitals were eligible for enrollment if they were ≤ 75 years, had symptoms typical of AMI lasting ≥ 20 minutes and unrelieved with nitroglycerin, presented within 6 hours of onset of symptoms and met electrocardiographic criteria.

ELECTROCARDIOGRAPHIC CRITERIA: Upward bowing (convex) ST-segment elevation >0.1 mV in ≥ 2 associ-

ated leads measured 60 ms beyond the J point was required for enrollment. The presence of Q waves did not exclude patients from treatment.

EXCLUSION CRITERIA: Factors that excluded patients from enrollment in the trial included: (1) any medical contraindication to thrombolysis or systemic anticoagulation; (2) diastolic blood pressure >120 mm Hg; (3) major surgical procedure or major trauma in chest, abdomen, cranium or spinal cord within 2 months; (4) any history of cerebrovascular accident or known intracerebral neoplasm, arteriovenous malformation or aneurysm; (5) recent cardiopulmonary resuscitation with clinically apparent rib fracture, flail segment or sternal instability; (6) vascular access in a noncompressible site (e.g., internal jugular or subclavian vein) placed within 72 hours of treatment; and (7) concomitant known disease likely to limit lifespan to <6 months in the absence of AMI or that might impair cooperation with the study.

PATIENT MANAGEMENT: We obtained informed consent as approved by the institutional human subjects review committee at each hospital (approval date, October 17, 1986). Treatment was initiated in the emergency department. Initially, the rt-PA dose was 150 mg given as 1 mg/kg to a maximum of 90 mg with an immediate bolus of 10% over the first hour, followed by continuous infusion of the remaining rt-PA over 5 hours. However, after the occurrence of an intracerebral hemorrhage in the ninth of 10 patients treated at the 150-mg dose, and a report of excess of intracerebral hemorrhage at this dose,¹³ the total dose was reduced to 100 mg. Subsequent patients received a bolus of 6 mg, followed by 54 mg in the first hour, 20 mg in the second, and 5 mg/hour in hours 3 to 6.

Continuous intravenous heparin (5,000 IU bolus and 500 IU/hour) was begun 1 hour after the start of the rt-PA infusion and was adjusted every 6 hours to maintain the partial thromboplastin time between 60 and 90 seconds for 96 hours. Creatine phosphokinase was determined every 4 hours during the first 24 hours. Coronary care unit staff performed assessment of bleeding and made neurologic observations. Decisions concerning additional therapy, including angioplasty and coronary artery bypass grafting, were made at the discretion of the attending physician. Patients received aspirin, 325 mg/day, starting on the day after rt-PA infusion.

ASSESSMENT OF VENTRICULAR FUNCTION AND INFARCT SIZE: Coronary arteriography and left ventriculography at 7 to 10 days after initial rt-PA therapy were recommended but not required. At 10 to 12 weeks after hospital discharge, ejection fraction measured by radionuclide ventriculography and infarct size measured by single-photon emission computed tomographic thallium-201 imaging were performed at the Seattle Veterans Administration Medical Center.³

CLINICAL DATA COLLECTION: The enrolling physician recorded initial baseline data, which were verified by the research nurse. These data included age and gender, presence of inclusion and exclusion criteria, highest systolic and diastolic blood pressures during the first hour, acute infarct location as determined by electrocardiography and the results of physical and neurologic exami-

TABLE 1 Reasons for Ineligibility for Thrombolytic Therapy in Patients with Acute Myocardial Infarction (n = 1,028)

Variable	No.	(%)
Ineligible patients	807	(78.5)
Single reason for ineligibility	332	(32.3)
Age >75	36	(3.5)
Presentation >6 hours	50	(4.9)
Nondiagnostic ECG	170	(16.5)
Contraindications	76	(7.4)
Two reasons for ineligibility	307	(29.9)
Age >75 and presentation >6 hours	19	(1.8)
Age >75 and nondiagnostic ECG	62	(6.0)
Age >75 and contraindications	30	(2.9)
Presentation >6 hours and nondiagnostic ECG	90	(8.8)
Presentation >6 hours and contraindications	14	(1.4)
Nondiagnostic ECG and contraindications	92	(9.0)
Three reasons for ineligibility	149	(14.5)
Age >75, presentation >6 hours, nondiagnostic ECG	42	(4.1)
Age >75, presentation >6 hours, contraindications	11	(1.1)
Age >75, nondiagnostic ECG, contraindications	49	(4.8)
Presentation >6 hours, nondiagnostic ECG, contraindications	47	(4.6)
Four reasons for ineligibility	16	(1.6)
Unknown	3	(0.3)

ECG = electrocardiogram.

nation. We also recorded the patient's clinical status at the time of entry. Hemodynamic status was indicated as stable, hypotensive (systolic blood pressure <90 mm Hg) or cardiogenic shock (systolic blood pressure <80 mm Hg with evidence of hypoperfusion). Additional data abstracted from the chart included time of chest pain onset, mode and time of arrival to the hospital, time of arrival of ambulance or paramedics (if used) and time of rt-PA administration. We assessed the patient's cardiac history before hospitalization; we noted prior AMI, angina, hypertension requiring treatment, current cigarette smoking, congestive heart failure and cardiac drug therapy, as well as prior angioplasty and coronary artery bypass grafting. Bleeding complications were documented in detail. In addition, partial thromboplastin time and creatine phosphokinase values were

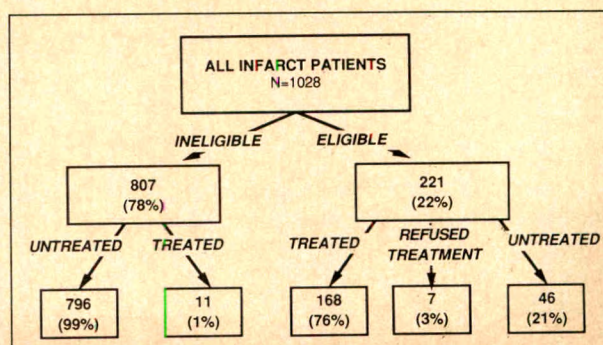


FIGURE 1. Eligibility for thrombolytic therapy and subsequent thrombolytic treatment in 1,028 consecutive acute myocardial infarction patients at 8 hospitals.

TABLE II Prevalence of Contraindications to Thrombolytic Therapy in Patients with Acute Myocardial Infarction (n = 1,028)

Contraindication	No.
Intracranial pathology	125
Recent surgery/trauma	59
Diastolic blood pressure >120 mm Hg	45
Comatose	40
Active bleeding	38
Unable to cooperate*	36
Renal disease	32
Recent cardiopulmonary resuscitation	14
Other medical reasons†	13
Recent central line placement	10
Terminal illness	8
Retinopathy	8
Aneurysm	4
Hepatic disease	3
Active peptic ulcer disease	2
One or more of these	335

* Dementia, psychiatric illness.
† Anemia (3), leukemia (2), thrombocytopenia (2), pancreatitis (2), breast cancer (1), pancytopenia (1), sepsis (1) and small bowel obstruction (1).

recorded. The dates of cardiac catheterization, coronary angioplasty and coronary artery bypass surgery were listed for patients undergoing these procedures. AMI was confirmed by enzymatic and electrocardiographic information. Finally, vital status at discharge was determined and cause of death was ascertained.

ANGIOGRAPHY: For those patients who underwent coronary angiography, an angiographic reading committee reviewed the films. The committee classified stenoses according to severity and location, and determined the number of diseased vessels. Collateral circulation to the distal bed of the infarct-related artery was graded on a scale of 0 to 3, as previously defined.¹⁴ Adequacy of blood flow in the infarct-related vessel was graded using standard criteria.¹⁵ Ejection fractions were determined using the centerline method.¹⁶

FOLLOW-UP: A 6-month and 1-year follow-up were accomplished by mail or by phone, or both. Vital status and interim coronary bypass surgery and coronary angioplasty were ascertained.

STATISTICAL METHODS: We used the chi-square statistic to test for statistical significance for categorical variables, and for continuous variables, we used the 2-tailed *t* test to determine statistical significance. Continuous variables were expressed as mean \pm 1 standard deviation. We used the product limit method to test for differences in long-term survival between anterior and inferior AMI.

RESULTS

Myocardial Infarction Registry: During the trial 1,028 patients with AMI were admitted to participating hospitals; 30 (3%) had only electrocardiographic evidence of AMI, 276 (27%) had only creatine phosphokinase elevation with MB fraction \geq 5% of the total, and 693 (67%) had both; 29 (3%) had missing information, but with clinical presentation were considered to be diagnostic of AMI. Two hundred twenty-one (22%) met

TABLE III Baseline and Outcome Variables for Patients Treated with rt-PA

No. of pts	160
Age (yrs)	58 \pm 10
Women	19%
Anterior AMI	38%
Inferior AMI	62%
Time to arrival (minutes)	94 \pm 65
Time to treatment (minutes)	141 \pm 169
Hemodynamically stable	89%
Cardiogenic shock	2%
Prior AMI	16%
Peak creatine phosphokinase	1954 \pm 1723
Time to peak creatine phosphokinase (hours)	15.3 \pm 11.7
Outcome variables	
14-day mortality—inferior	3%
14-day mortality—anterior	10%
One-year survival—inferior	96%
One-year survival—anterior	85%
Infarct artery patency	75%
Angiographic ejection fraction—inferior (%)	54 \pm 10
Angiographic ejection fraction—anterior (%)	48 \pm 11
Radionuclide ejection fraction—inferior (%)	56 \pm 10
Radionuclide ejection fraction—anterior (%)	43 \pm 17
Infarct size	
(% infarcted left ventricle)—inferior	10 \pm 10
(% infarcted left ventricle)—anterior	19 \pm 12

AMI = acute myocardial infarction; rt-PA = recombinant tissue-type plasminogen activator.

study criteria for rt-PA (Figure 1). Under the study protocol, 160 patients (72%) received rt-PA, 8 received thrombolytic therapy outside the trial, and 7 refused thrombolytic treatment. Thus, 175 eligible patients (79%) were correctly identified for treatment by emergency physicians. Forty-six patients (21%) were not treated. The reasons these patients did not receive thrombolytic therapy were not specified in the records. Only 11 (1%) of 807 patients who were ineligible under study criteria were treated with thrombolysis, and none was treated by a participating emergency physician.

The reasons for the ineligibility of 807 patients are listed in detail in Table I. Overall, 265 (26%) were \geq 75 years, 289 (28%) presented after 6 hours of chest pain, and 568 (56%) had nondiagnostic electrocardiograms. In addition, 335 patients (33%) had \geq 1 contraindications to thrombolytic therapy. Contraindications are specified in Table II.

Recombinant tissue plasminogen activator treatment trial: Of the 160 patients in the trial, 157 (98%) had documented AMI, and of the 3 without documented AMI, 1 patient had unstable angina, whereas the other 2 had neither enzymatic nor electrocardiographic evolution consistent with AMI despite presenting with compatible symptoms and ST elevation. The mean peak creatine phosphokinase was $2,209 \pm 1,737$ IU/liter in 151 surviving patients and the average time to the peak value was 15.6 ± 11.8 hours.

Table III lists baseline and outcome variables for patients treated in the present study. Patients treated in the emergency department rt-PA trial were treated 141 ± 69 minutes after symptom onset, on average 68 minutes faster than in the Western Washington Intravenous Streptokinase Trial,⁸ where treatment was started in the

coronary care unit 209 ± 84 minutes after symptom onset ($p < 0.0001$). Mean time from arrival to thrombolysis in the present study was 55 ± 27 minutes (range 17 to 155 minutes), with a median of 52 minutes. Despite a concerted effort to treat patients within 60 minutes of hospital arrival, in 36.7% of rt-PA trial patients, rt-PA was started after 60 minutes.

MORTALITY: There were 9 (5.6%) deaths during the first 14 days after treatment; 3 patients died of cardiogenic shock, 2 of arrhythmia, 1 of cardiac rupture, 1 of AMI complicated by previously undiagnosed leukemia, 1 during bypass surgery, and 1 of recurrent AMI after hospital discharge. There was an additional cardiac death at day 21, which resulted in a 42-day mortality of 6.2%. Patients who died within 14 days did not differ from survivors with respect to age, sex or prior AMI. Mortality for patients with anterior and inferior AMI was 9.8 and 3.0%, respectively ($p = 0.069$).

Six-month follow-up has been completed for 148 of 151 (98%) surviving patients, and 12-month follow-up has been completed for 139 of 147 (95%) surviving patients. The average follow-up time was 364 ± 78 days. Four patients are known to have died in the interval between 14 days and 6 months and 1 is known to have died after 6 months. Therefore, 1-year survival by life-table methods was 92%. All late deaths were due to cardiac causes. One-year survival for anterior AMI was 85%, whereas 1-year survival for inferior AMI was 96% ($p = 0.03$ by the log-rank statistic).

CARDIAC CATHETERIZATION: Cardiac catheterization was performed on 145 (91%) patients 5 ± 3 days (range 0 to 19 days) after infarction; 143 (99%) films were available for review. These data are listed in Table III. The infarct-related coronary artery was the left anterior descending in 36%, the right in 45%, and the circumflex in 19%. The overall patency rate was 75%: 78% for anterior infarction and 74% for inferior infarction ($p = 0.59$). The average residual percent diameter stenosis for patients without total occlusion was $74 \pm 20\%$. There were 112 films (78%) that had left ventricular angiograms of adequate quality to determine ejection fractions, as listed in Table III.

LATE EJECTION FRACTION AND INFARCT SIZE: Radionuclide ejection fraction and thallium infarct size measurements were completed in 100 (62%) patients at 11.3 ± 4.4 weeks after AMI. These data are listed in Table III.

TREATMENT AFTER ACUTE MYOCARDIAL INFARCTION: During the first 14 days after AMI, 33 (21%) patients underwent coronary artery bypass graft surgery, and 31 (19%) underwent coronary balloon angioplasty; by 1 year, 24% had coronary artery surgery and 20% had coronary angioplasty. There was 1 surgical death. The duration of hospitalization for surviving patients was 10 ± 7 days. In comparison, during the first 14 days after AMI, bypass surgery and angioplasty were performed in 7 and 6%, respectively, of patients in the intravenous streptokinase trial;⁸ 27% had a revascularization procedure in the first year after AMI.

COMPLICATIONS OF RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR TREATMENT: Bleeding was reported in 44 pa-

tients (28%), but most of these incidents were minor; 6 (4%) patients required transfusions. Gross hematuria and hematoma were reported in 6 (4%) and 10 (6%) patients, respectively. Intracerebral hemorrhage, the major complication of therapy, occurred in 3 patients (1.9%, 95% confidence interval 0.4 to 5.5%); 1 patient received the 150-mg dose of rt-PA and 2 received the 100-mg dose. None of these patients died. One patient was left with a mild residual neurologic deficit, while 2 had complete neurologic recovery at 6-month follow-up.

DISCUSSION

Our primary objective was to evaluate initiating administration of rt-PA for AMI in the emergency department.¹⁷ In previous trials, cardiologists have decided on thrombolytic therapy; however, this policy increases the time from presentation to treatment,¹² which may decrease the benefit of clot lysis on left ventricular preservation.¹⁸ We are not aware of any study that has evaluated the performance of emergency physicians starting thrombolytic therapy.

In this study, emergency physicians failed to offer thrombolytic therapy to 46 of 221 (21%) of eligible patients. This proportion is probably higher at hospitals where the staff is not as familiar with thrombolytic therapy. Thus, one strategy to increase the numbers of patients treated is to educate physicians about thrombolytic therapy and to offer treatment to all eligible patients. AMI was subsequently ruled out in only 3 of 160 patients (2%) treated by emergency physicians. The effectiveness of emergency department triage was also seen in the small number of patients (11 of 807, 1%) ineligible by study criteria, who subsequently had thrombolytic therapy given by cardiologists. The inci-

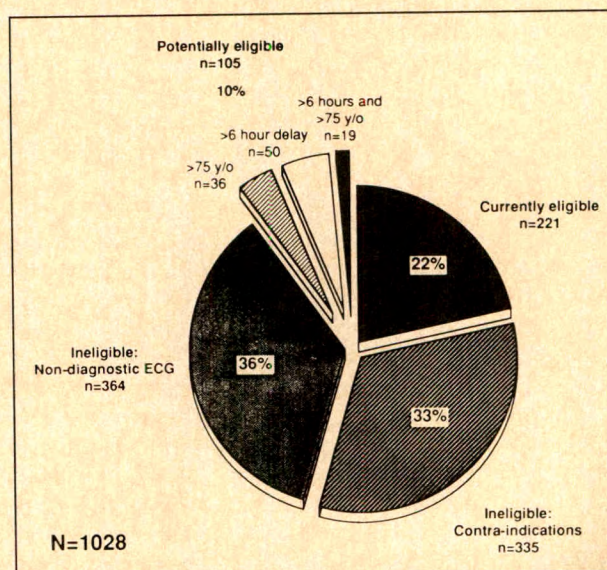


FIGURE 2. Distribution of patients eligible and ineligible for thrombolytic therapy, and reasons for ineligibility among 1,028 consecutive acute myocardial infarction patients at 8 hospitals. Shown in exploded portion are patients with only age or duration of chest pain exclusion criteria, who are potentially eligible for thrombolytic therapy. ECG = electrocardiogram.

dence of serious bleeding complications was similar to that seen in other trials of rt-PA.^{6,10} Although the rate of intracerebral hemorrhage is high, it is based on 3 events and statistically is not significantly different from the rate reported in a recent larger trial.¹⁰

A randomized trial was not performed because, during the planning phase of the trial (1986), the evidence favoring thrombolytic therapy made a placebo-controlled trial in our community unethical, and resources were insufficient to enter the large numbers of patients required to perform a randomized trial of rt-PA versus another thrombolytic agent. We have therefore compared the results of the present study with our earlier randomized trial of intravenous streptokinase.⁸ This trial ended 4 months before the start of the rt-PA trial and included the 8 hospitals in the current study. The baseline demographic and clinical features of the 2 patient populations were nearly identical. Given the limitations imposed by historical comparisons, we found that emergency department diagnosis and treatment shortened the time from hospital admission to therapy by an average of 68 minutes. The reasons for this decrease between the 2 trials have been discussed.¹⁹ Sharkey et al¹² found on average a 70-minute delay between emergency department arrival and thrombolytic therapy, with 34 minutes additional time taken by transporting patients to the coronary care unit.

A second objective was to define the proportion of patients who were eligible for thrombolytic therapy, and the prevalence of contraindications in a complete population of patients with AMI. Most trials report only the results for patients who were treated with thrombolytic therapy; the impact of treatment among all patients with AMI has been less clear. In the studies that recorded the number of all AMI patients, the proportion eligible for therapy ranged from 23 to 51%,^{4-6,20,21} yet none specified detailed reasons for patient exclusion. This variability is due in part to differences in exclusion criteria. We used the criteria currently stated in the package insert for intravenous treatment with rt-PA and thus our study probably closely reflects current accepted practice.

Figure 2 shows the potential increases in the proportion of AMI patients eligible for thrombolytic therapy in our study; 335 (33%) had contraindications that place them at very high risk from thrombolytic therapy. Another 364 patients (36%) had nondiagnostic electrocardiograms. Because 65 to 75% of these patients do not have AMI,^{22,23} treating them with thrombolytic therapy would expose many patients without infarction to significant hemorrhagic risks. Additionally, the benefit of treating AMI patients with nondiagnostic electrocardiograms has not been demonstrated conclusively.^{4,9} After excluding these patients, we found 326 patients (32% of all patients) potentially eligible for thrombolytic therapy, 105 (48%) more than were eligible under current guidelines. Thirty-six of these patients had been excluded solely because of age, 50 solely because of delay in presentation, and 19 because of both. Recent studies suggest significant benefits from thrombolytic therapy in these patients, who should not be excluded from ther-

apy for these reasons alone.⁹ Thus, based on this experience, at most 1 in 3 patients with AMI appears to be eligible for thrombolytic therapy.

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APPENDIX

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Ability of Calcium-Entry Blockade by Felodipine To Disclose Different Pathogenetic Mechanisms Behind Hyperventilation-Induced Myocardial Ischemia in Men

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To verify that myocardial ischemia occurring during either the overbreathing or recovery phase of the hyperventilation test is based on different pathogenetic mechanisms, 2 consecutive series of patients, selected on the basis of their response to a run-in hyperventilation test, were studied. Group I comprised 15 patients who developed ST-segment depression early during overbreathing, whereas group II consisted of 12 patients showing ST-segment depression late during the recovery phase. A single oral dose of felodipine 10 mg or of placebo was administered on 2 consecutive days according to a randomized, double-blind, crossover design, and the hyperventilation test was repeated, on both days of the study, 3 to 5 hours after drug intake. In group I, ST-segment depression occurred after placebo in all patients during overbreathing, with an increase in rate pressure product (from 112 ± 31 at baseline to 168 ± 55 mm Hg \times beats/min/100 at the onset of ST-segment depression; $p < 0.01$). After felodipine, 13 patients continued to show ST-segment depression during overbreathing, together with an increase in rate pressure product (from 107 ± 24 at baseline to 158 ± 46 mm Hg \times beats/min/100 at the onset of electrocardiographic changes; $p < 0.01$). In group II, all 12 patients showed ST-segment depression during recovery after placebo, with a rate pressure product comparable to baseline conditions (112 ± 35 at baseline vs 102 ± 27 mm Hg \times beats/min/100 at the onset of ST-segment depression; difference not significant). After felodipine, no patient developed ST-segment depression or chest pain. These findings confirm that early hyperventilation-induced ST-segment depression is related to increased oxygen consumption, which cannot be prevented by felodipine. On the other hand, felodipine is highly effective in preventing delayed ischemia, which is due to a primary reduction in coronary blood flow.

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The hyperventilation test has been used to provoke myocardial ischemia in patients with coronary artery disease.¹⁻⁴ Ischemic electrocardiographic changes may occur during either the overbreathing or the recovery phases of the test and are probably related to different pathogenetic mechanisms. Myocardial ischemia observed early during overbreathing has been attributed to increased oxygen demand in patients with poor coronary reserve, whereas delayed ischemia observed during the recovery phase of the test is probably due to a primary reduction in coronary blood flow.⁵ To verify that hyperventilation-induced myocardial ischemia is based on different pathogenetic mechanisms in relation to the phase of the test in which it occurs, we investigated the effect of felodipine, a new vasoselective dihydropyridine calcium antagonist, in patients with an early or delayed positive response to the test. Felodipine has the potential to differentiate between these 2 pathogenetic mechanisms, because it is a powerful inhibitor of coronary vasoconstriction and does not have a major influence on myocardial oxygen consumption.^{6,7}

METHODS

Patient selection: We studied 97 consecutive patients with a clinical history of angina pectoris and angiographically documented coronary artery disease. All patients underwent a hyperventilation test. Among them, 14 had clinical characteristics of variant angina and hyperventilation-induced ST-segment elevation, whereas 27 showed hyperventilation-induced ST-segment depression, occurring during the overbreathing phase in 15 patients and during the recovery phase in the remaining 12. Our study population consisted of the 15 patients showing ST-segment depression during overbreathing (group I) and of the 12 patients who developed ST-segment depression during recovery (group II). The hyperventilation test was not performed in patients with chronic pulmonary disease, left bundle branch block, clinical conditions that did not justify temporary withdrawal of antianginal therapy, such as crescendo angina, prolonged chest pain at rest, poor response to nitroglycerin, severe ventricular arrhythmias or left ventricular failure during anginal attacks. All patients were informed of the study procedure and gave their consent for participation in the study. The protocol was approved by the appropriate institutional committees.

Hyperventilation test: The hyperventilation test was performed by asking the patients to breathe as deeply and rapidly as possible (≥ 30 respirations per minute) for 5 minutes. A 12-lead electrocardiogram and blood pressure (cuff) were recorded at rest, before starting overbreathing, every minute during the test, and during at least the first 10 minutes of the recovery phase. An estimate of myocardial oxygen consumption was made from the rate pressure product, obtained by multiplying heart rate and systolic blood pressure (beats/min \times mm Hg). A positive test response was defined as an electrocardiographic change (ST-segment depression >1 mm for 0.08 second after the J point), with or without chest pain, developed during the overbreathing or the recovery phase of the test. During the test and the recovery phase, the time to onset of 1-mm ST-segment depression was recorded.

Study protocol: The 2 series of, respectively, 15 (group I) and 12 (group II) patients, selected on the basis of the aforementioned criteria, were enrolled for a randomized, double-blind, crossover study. One tablet of felodipine 10 mg or matching placebo was administered on 2 consecutive days at 6:00 A.M. Hyperventilation tests were performed 3 to 5 hours after drug or placebo administration in the fasting state. Beta-adrenergic blocking agents were gradually withdrawn ≥ 72 hours before the initiation of the study, whereas nitrates and calcium antagonists were discontinued 24 hours before; only sublingual nitroglycerin was used during the latter period, and a minimum of 2 hours was allowed to elapse before testing was started, if the drug had been used.

Felodipine plasma concentration: Blood samples (8 ml) for analysis of felodipine plasma concentrations were taken by venipuncture immediately before each hyperventilation test. Plasma was separated by centrifugation at 3,000 rpm for 10 minutes, stored at -20°C , and analyzed at the Department of Analytical Chemistry, AB, Hässle, Sweden.

Coronary arteriography and great cardiac vein flow measurements: Selective coronary arteriography was performed in multiple views using the Sones or the Judkins technique after premedication with 10 mg diazepam. Left ventriculography was performed in the right anterior oblique projection before coronary arteriography. Narrowing of $>50\%$ of ≥ 1 coronary artery was considered significant coronary artery disease. When a significant lesion was noted, the vessel was filmed again after sublingual administration of nitroglycerin. In 2 patients, 1 from each group, with isolated lesions of the left anterior descending artery, measurements of great cardiac vein flow (GCVF) were obtained by the thermolilution technique—during 2 further hyperventilation tests—before and after the administration of felodipine. A multithermistor catheter was introduced in the coronary sinus and advanced until the distal thermistor was well within the great cardiac vein. Room temperature normal saline solution was injected at the rate of 55 ml/min and blood flow from the great cardiac vein was computed by the formula: $\text{GCVF} = \text{FI} \times 1.08 \times (\text{TB} - \text{TI}) / (\text{TB} - \text{TMGCVF}) - 1$, where FI is the volume flow of indicator per minute; 1.08 is the constant of nor-

TABLE I Clinical and Angiographic Characteristics of Men Showing Hyperventilation-Induced ST-Segment Depression During Overbreathing (Group I) or During Recovery (Group II)

	Group I (n = 15)	Group II (n = 12)
Mean age (years)	56 \pm 5	55 \pm 8
Cigarette smoking	6	8
Previous AMI	5	3
Duration of angina (mos.)	6 \pm 5	8 \pm 7
Type of angina		
Rest	2	6
Effort	6	2
Rest and effort	7	4
No. of narrowed coronary arteries		
1	4	6
2	6	2
3	5	4
Ejection fraction (%)	63 \pm 11	60 \pm 13

AMI = acute myocardial infarction.

mal saline solution; and TB, TI and TMGCVF are the temperatures of blood, indicator, and mixture of blood and indicator in the great cardiac vein, respectively. Mean arterial pressure (MAP) was continuously measured. An index of arterial regional coronary resistance (ARCR) was calculated according to the formula: $\text{ARCR} = \text{MAP}/\text{GCVF}$. Following the standard protocol, hyperventilation tests were carried out under control conditions and repeated 10 minutes after intravenous administration of 1.25 mg of felodipine. The electrocardiographic parameters were recorded as described before. GCVF measurements were obtained at rest and at the onset of ischemia. When the hyperventilation test was performed after felodipine, the measurement was obtained at the same time at which ischemia occurred during the control study.

Statistical analysis: The Yates corrected chi-square test was used to compare all the baseline characteristics of the 2 groups. Continuous data are presented as mean \pm standard deviation and the statistical analysis was performed by Student *t* test for paired and unpaired data, as appropriate. A *p* value <0.05 was considered statistically significant.

RESULTS

Patient characteristics: Patient characteristics, including age, smoking habits, duration and type of angina and the presence of prior myocardial infarction, were similar in groups I and II. The 2 groups were also similar with respect to the extent of coronary artery disease and ejection fraction (Table I).

Hyperventilation test after the administration of placebo and felodipine: **GROUP I:** The results were computed on 14 patients; 1 patient was withdrawn because of a prolonged episode of angina at rest during the placebo period. Study termination was then required and antianginal therapy was immediately started. After placebo administration, the hyperventilation test induced ST-segment depression during overbreathing in all 14 patients and was accompanied by chest pain in 10. The onset of ST-segment depression occurred after 172 ± 93 seconds of overbreathing and the mean duration of the

electrocardiographic changes was 200 ± 84 seconds. The electrocardiographic changes, similar to those obtained during the run-in test, involved anterior leads in 10 patients and inferolateral leads in 4. Hyperventilation-induced ischemic attacks subsided spontaneously in all patients. The rate pressure product increased from a baseline value of 112 ± 31 to 168 ± 55 mm Hg \times beats/min/100 at the onset of ST-segment depression ($p < 0.01$), with a peak value of 170 ± 50 mm Hg \times beats/min/100 at the end of overbreathing ($p < 0.01$).

After felodipine administration, 13 out of the 14 patients continued to have a positive response to the hyperventilation test during overbreathing, and the electrocardiographic changes were accompanied by anginal pain in 11 patients. The onset of ST-segment depression occurred after 161 ± 83 seconds of overbreathing, involving the same leads as during the run-in period test, and the mean duration of electrocardiographic changes was 168 ± 79 seconds. The rate pressure product increased from a baseline value of 107 ± 24 to 158 ± 46 mm Hg \times beats/min/100 at the onset of electrocardiographic changes ($p < 0.01$), with a peak value of 160 ± 40 mm Hg \times beats/min/100 at the end of overbreathing ($p < 0.01$). No significant differences in rate pressure product values were observed between the hyperventilation tests performed after either placebo or felodipine administration. The mean plasma concentration

of felodipine was 17.3 ± 12.2 nmol/liter. No adverse effects were reported during the study.

GROUP II: After placebo administration, hyperventilation induced ST-segment depression during the recovery phase in all 12 patients and the electrocardiographic changes (anterior leads in 9 patients, inferolateral leads in 3) were similar to those obtained during the run-in test, and were accompanied by anginal pain in 7 patients. The onset of ST-segment depression was reached 109 ± 57 seconds after the end of overbreathing, and the mean duration of electrocardiographic changes was 138 ± 65 seconds. Hyperventilation-induced ischemic attacks subsided spontaneously in 9 patients, whereas they were relieved by the administration of nitroglycerin (0.3 mg sublingually) in 3 patients. The mean rate pressure product at baseline was 112 ± 35 mm Hg \times beats/min/100 and increased to 148 ± 37 mm Hg \times beats/min/100 ($p < 0.05$) at the peak of overbreathing, whereas at the onset of electrocardiographic changes the mean rate pressure product was approaching baseline values (102 ± 27 mm Hg \times beats/min/100; difference not significant). After the administration of felodipine, none of the patients developed either chest pain or ST-segment changes during the hyperventilation test; the rate pressure product at baseline was 108 ± 33 mm Hg \times beats/min/100 and increased to 152 ± 30 mm Hg \times beats/min/100 at the peak of overbreathing ($p < 0.01$).

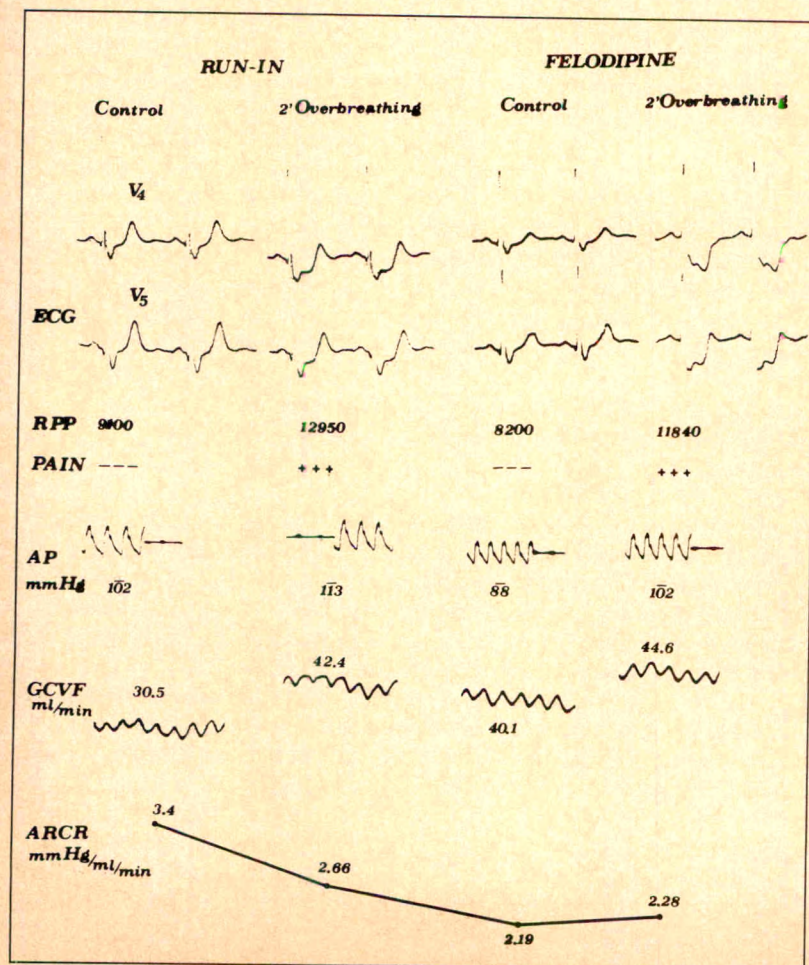


FIGURE 1. Early ST-segment depression in a group I patient during overbreathing: Electrocardiographic (ECG), rate pressure product (RPP) and hemodynamic changes under control conditions and after 2 minutes (2') of overbreathing during run-in (left) and after the intravenous administration of 1.25 mg of felodipine (right). AP = arterial pressure tracings (numbers refer to mean arterial pressure); ARCR = anterior regional coronary resistance; GCVF = great cardiac vein flow; + = presence; - = absence.

The mean felodipine plasma concentration was 14.6 ± 8.9 nmol/liter. No adverse effects were reported during the study.

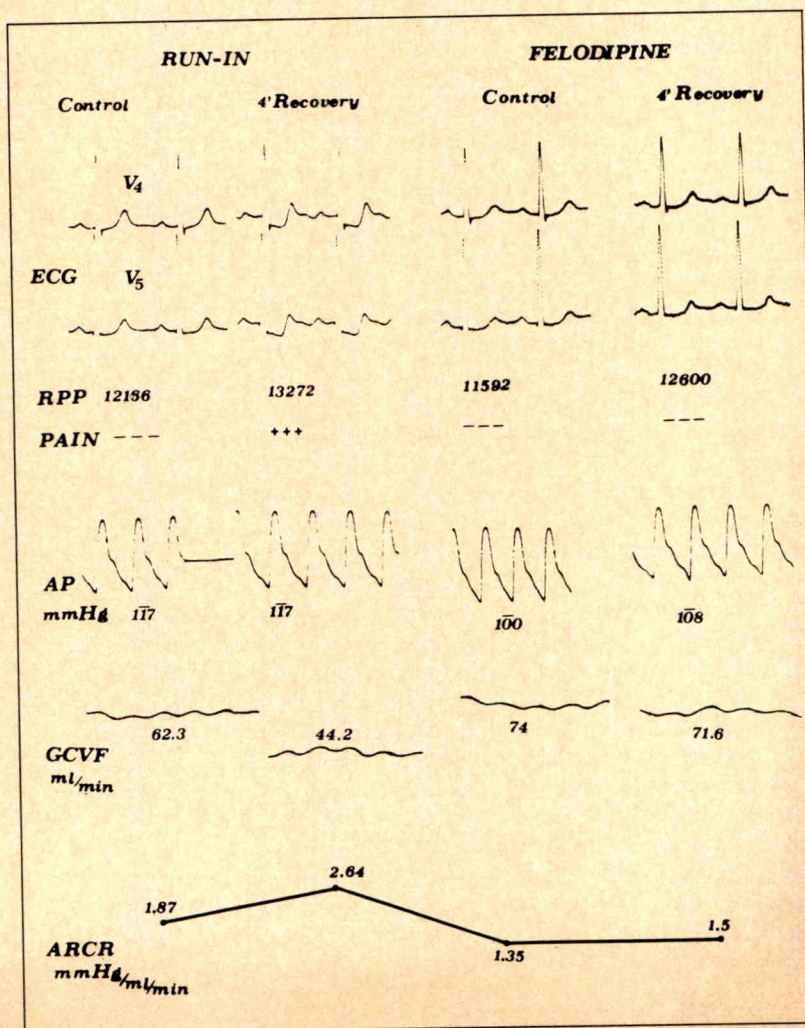
Great cardiac vein flow measurements: The effect of felodipine on coronary circulation was evaluated in 2 patients (1 from each group) with an isolated left anterior descending artery stenosis. The group I patient (Figure 1), who developed ST-segment depression and chest pain early during overbreathing, showed an increase of GCVF from a baseline value of 30.5 to 42.4 ml/min at the onset of ischemia. The coronary resistance of the area supplied by the stenotic left anterior artery decreased from 3.4 mm Hg/ml/min at baseline to 2.66 mm Hg/ml/min at the onset of ST changes. After felodipine administration, the patient continued to show hyperventilation-induced ST-segment depression accompanied by anginal pain. GCVF at rest was consistently higher than control values (40.1 vs 30.5 ml/min), whereas the anterior coronary resistance was reduced (2.19 vs 3.4 mm Hg/ml/min). In comparison with values before treatment, no significant differences in GCVF were observed at the onset of electrocardiographic changes or at the peak of overbreathing. The group II patient (Figure 2) who developed ST-segment depression during recovery also experienced angina at

the onset of electrocardiographic changes. GCVF decreased from a baseline value of 62.3 to 44.2 ml/min at the onset of electrocardiographic changes, whereas coronary resistance of the area supplied by the stenotic left anterior descending artery was increased (from 1.87 to 2.64 mm Hg/ml/min). The effects of felodipine administered intravenously were assessed 10 minutes later. Baseline GCVF was consistently higher and anterior coronary resistance lower than values before treatment (74 vs 62.3 ml/min; 1.35 vs 1.87 mm Hg/ml/min). Hyperventilation did not induce either angina or ST-segment depression, and GCVF and anterior coronary resistance were not significantly modified.

DISCUSSION

Hyperventilation-induced ST-segment depression in patients with coronary artery disease: Although subjects without apparent heart disease may show pseudoischemic electrocardiographic changes during hyperventilation,^{8,9} these false positive responses are different from those observed when the hyperventilation test is performed in patients with coronary artery disease.⁵ ST-segment elevation is the classic electrocardiographic response when the hyperventilation test is performed in patients with variant angina. However, it has been re-

FIGURE 2. Late ST-segment depression in a group II patient during recovery: Electrocardiographic (ECG), rate pressure product (RPP) and hemodynamic changes under control conditions and at the fourth minute of recovery during run-in (left) and after the intravenous administration of 1.25 mg of felodipine (right). Abbreviations as in Figure 1.



ported that, in patients with coronary artery disease, hyperventilation may induce ST-segment depression during either the overbreathing phase or the recovery phase of the test. Early ST-segment depression occurring during overbreathing is associated with an increase in oxygen demand, whereas that occurring later during the recovery phase is probably related to a primary reduction in coronary blood flow.⁵ The distinction between early and late electrocardiographic changes is usually feasible according to the time of onset of 1-mm ST-segment depression. In the present series, group I patients developed unequivocal ischemic electrocardiographic changes during overbreathing, when the rate pressure product was significantly higher than during control conditions; on the other hand, group II patients did not develop ischemia when the rate pressure product was increased; but they did during the recovery phase, when the rate pressure product was approaching baseline values. Coronary hemodynamic data collected in 2 representative patients directly support this hypothesis: the group I patient developed ischemia, notwithstanding an increased coronary blood flow and reduced coronary resistance, whereas the development of ischemia in the group II patient was associated with a reduction in coronary blood flow well below baseline values and with a corresponding increment in regional coronary resistance.

Effects of felodipine on early and delayed hyperventilation-induced ischemia: The effects of felodipine on hyperventilation-induced electrocardiographic changes were dramatically different in the 2 groups of patients. Whereas early hyperventilation-induced ST-segment depression was essentially unaffected by the drug, delayed ST-segment depression was totally prevented. This difference in response to the pharmacologic test may disclose the different pathogenetic mechanisms underlying hyperventilation-induced myocardial ischemia. Early ischemia occurred together with increments in oxygen demand, suggesting a reduced coronary reserve in patients showing this response to the test. The direct measurements of coronary blood flow performed during hyperventilation in 1 patient of group I did not show any increment in coronary resistance. Felodipine neither reduced the values of the determinants of myocardial oxygen consumption nor increased blood supply during overbreathing; consequently, the electrocardiographic response to hyperventilation remained essentially unchanged. On the other hand, delayed ischemia occurred without increments of myocardial oxygen consumption in patients of group II, and the direct measurements of coronary blood flow during hyperventilation performed in 1 patient showed that ischemia occurred together with an increase in coronary resistance. Felodipine prevented electrocardiographic changes by inhibiting the hyperventilation-induced coronary vasoconstriction.

The coronary dilating activity of felodipine has been shown in patients with coronary artery disease^{10,11} and its efficacy in preventing coronary spasm has been dem-

onstrated in variant angina.⁶ The present study confirms that felodipine induces coronary vasodilation and prevents abnormal coronary vasoconstriction. The efficacy of a vasoselective calcium antagonist in inhibiting delayed hyperventilation-induced myocardial ischemia is a further indirect proof that the pathogenetic mechanism behind this ischemic pattern is a primary reduction of coronary blood flow. However, the lack of activity of felodipine in conditions of increased oxygen demand is puzzling in the light of the positive results obtained with this drug during exercise testing.^{12,13} This apparent discrepancy may be partly explained by the differing efficacy of calcium antagonists in demand-related ischemia depending on the contribution of coronary vasomotion to the reduction in coronary reserve.¹⁴ Our data suggest that patients with a positive response to hyperventilation during overbreathing have a reduced coronary reserve that is not susceptible to pharmacologic manipulation with a dihydropyridine calcium antagonist. Similar results have been obtained with nifedipine, which has also been shown to be ineffective in preventing early hyperventilation-induced ischemia, whereas propranolol, a drug that reduces oxygen demand, totally prevents this ischemic pattern.⁵

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Long-Term Prognosis of Myocardial Ischemia Detected by Holter Monitoring in Peripheral Vascular Disease

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To assess the long-term prognostic significance of myocardial ischemia, as measured by ambulatory electrocardiographic monitoring, in patients with occlusive peripheral arterial disease, 176 eligible patients scheduled for elective peripheral arterial surgery at Brigham and Women's Hospital were prospectively studied. All patients were monitored preoperatively without alterations to baseline medications. Prospective follow-up was obtained during routine medical care as provided by blinded, independent physicians and by subsequent telephone contact with the patients. Thirty-two patients (18%) had a total of 75 episodes of myocardial ischemia, 73 (97%) of which were asymptomatic. During a mean follow-up period of 615 days, there were 9 cardiac deaths, 1 occurring in-hospital after peripheral vascular surgery, and 13 nonfatal myocardial infarctions, 4 occurring in-hospital after peripheral vascular surgery. Cardiac events occurred in 12 of 32 patients with ischemia (38%), including 6 cardiac deaths, and in 10 of 144 patients without ischemia (7%), including 3 cardiac deaths (risk ratio 5.4, 95% confidence interval 2.6 to 11.4). The sensitivity of ischemia was 55%, the specificity was 87%, the positive predictive value was 38%, and the negative predictive value was 93%. In a multivariate Cox proportional-hazards model controlling for age, gender, coronary risk factors, history of angina, myocardial infarction, coronary artery disease and antianginal medications, the presence of ischemia was the only independent predictor of outcome. In patients with peripheral arterial disease, who often are unable to perform adequate exercise testing, ambulatory monitoring for myocardial ischemia is a significant independent predictor of 1- to 2-year prognosis.

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In patients with coronary artery disease, multiple studies have shown a strong correlation between ST depression detected by ambulatory monitoring and other markers of myocardial ischemia, such as treadmill exercise testing, thallium and radionuclide imaging, and coronary angiography.¹⁻⁴ In addition, several studies have demonstrated that ischemia detected by ambulatory monitoring provides an independent, incremental contribution to prognosis in patients with stable and unstable angina pectoris,⁵⁻⁷ in patients with prior myocardial infarction¹ and in a cohort of asymptomatic elderly men.⁸

Most previous prognostic studies involving ambulatory monitoring for ischemia have concentrated on patients who underwent treadmill exercise testing. One of the insights gained from ambulatory monitoring trials, however, is that ischemia occurs at cardiac rates far below those achieved during exercise.⁹ This observation makes ambulatory monitoring a reasonable alternative in patients with peripheral arterial disease, because such patients are at increased cardiac risk but are unable to perform standard exercise tests.^{10,11}

We recently showed that preoperative myocardial ischemia detected by ambulatory monitoring provided independent, incremental information toward predicting in-hospital postoperative cardiac events in patients undergoing peripheral arterial surgery.¹¹ We have now followed this cohort of patients for a mean of 615 days to determine if preoperative ischemia also predicts late adverse cardiac outcome in the same population.

METHODS

Patient selection: As reported previously,¹¹ we screened 274 patients who were scheduled to undergo carotid, aortic/renal or femoral arterial surgery between September 1987 and July 1988, and, of these, 176 had electrocardiograms suitable for monitoring, were not operated on emergently and gave informed consent. A detailed history and physical examination was recorded by 1 of the investigators, and all patients were assigned to a cardiac risk index class.¹² In addition, all patients were evaluated preoperatively by independent cardiologists and judged able to undergo elective surgery. Exercise treadmill tests were performed at the discretion of the evaluating cardiologist, whenever the patient's physical state allowed for adequate exercise. In all, only 23 patients attempted exercise tests; 3 patients had positive test results, and 20 had negative test results; only 3 of these 20 achieved 85% of their

TABLE I Summary of 22 Deaths and Nonfatal Myocardial Infarctions

Pt	Age (yr) & Sex	Cardiac Event	In-Hospital	Days After Monitoring	Preoperative Ischemia Present
Death					
1	64, M	Death	+	9	+
2	64, M	Death	0	47	0
3	81, F	Death (sudden)	0	61	+
4	86, F	Death	0	92	+
5	71, M	Death (sudden)*	0	161	+
6	71, F	Death	0	300	0
7	64, M	Death (sudden)	0	390	+
8	68, M	Death	0	581	0
9	65, M	Death	0	613	+
MI					
1	78, F	MI (asymptomatic)	+	1	+
2	68, F	MI (asymptomatic)	+	2	+
3	69, M	MI	+	2	+
4	81, M	MI	0	30	0
5	63, F	MI (asymptomatic)	0	61	0
6	66, M	MI	0	165	+
7	63, M	MI	0	240	0
8	63, M	MI	0	441	+
9	78, M	MI	0	467	0
10	64, M	MI	0	626	+
11	78, M	MI	0	667	0
12	43, M	MI	0	686	0
13	67, M	MI	0	785	0

* Patient also had an asymptomatic MI in-hospital on postoperative day 2.
 MI = myocardial infarction; + = yes; 0 = no.

target heart rate. Of the 153 patients who were not exercised, 86 (56%) had symptomatic claudication at low exercise levels, or had amputations.

Ambulatory monitoring: As previously reported,¹¹ all patients wore a calibrated, Oxford Medilog frequency-modulated recorder (Clearwater, Florida) with 2 bipolar leads attached to exploring electrodes, for 24 to 48 hours before elective vascular surgery. Chest electrodes were placed to detect signals from an inferior and a lateral lead. For convenience only, 81% of patients were monitored as in-patients, and 91% were monitored with-

in 48 hours of elective surgery. Baseline medications were not changed. Two patients who had excessive monitor signal noise precluding tape interpretation were excluded. A structured diary was used to record symptoms and times.

Tapes were analyzed using a technician-interactive Cardiodata Mark IV computer (Northborough, Massachusetts), with manual confirmation by a physician blinded to computer reading and patients' clinical data. Discordance between reader and computer was reviewed manually by a third blinded reader and resolved

TABLE II Univariate Correlates of Cardiac Events (Death or Infarction)

	Event (%)		Significance Level	
	Present (n = 22)	Absent (n = 154)	Univariate	Multivariate
Age > 69 years	10 (45)	56 (36)	NS	NS
Male sex	16 (73)	108 (70)	NS	NS
Cigarette smoker	22 (100)	142 (92)	NS	NS
History of systemic hypertension	15 (68)	80 (52)	NS	NS
Cholesterol (> 240 mg/dl)	11 (50)	75 (49)	NS	NS
Family history of CAD	3 (14)	32 (21)	NS	NS
Diabetes mellitus	6 (27)	30 (19)	NS	NS
≥2 cardiac risk factors	20 (91)	125 (81)	NS	NS
Prior angina	9 (41)	39 (25)	NS	NS
History of MI	7 (32)	41 (27)	NS	NS
History of CAD	13 (59)	57 (37)	<0.05	NS
Antianginal medications	10 (45)	59 (38)	NS	NS
Ambulatory ischemia	12 (55)	20 (13)	<0.0001	<0.0001

* Prior myocardial infarction, positive exercise test, coronary artery surgery, angina pectoris or CAD documented by angiography.
 CAD = coronary artery disease; MI = myocardial infarction; NS = not significant.

by consensus. Episodes of ST-segment depression that met the following criteria were printed: planar or downsloping ST depression or ≥ 1 mm (compared with baseline) persisting 0.06 second beyond the J point, and persisting in consecutive beats for >60 seconds. The duration of an episode was defined as the number of minutes of ≥ 1 mm ST depression. A separate episode was recorded when the electrocardiogram returned to baseline for at least 3 minutes.

Follow-up: Patients were followed to hospital discharge by independent cardiologists blinded to monitor results. Subsequently, patients or their primary physicians of record, or both, were contacted by telephone between December 1989 and January 1990. Information obtained included occurrence of death, myocardial infarction or any hospitalization since elective vascular surgery. All hospitalizations were investigated by obtaining admission diagnoses, procedures and discharge diagnoses from the hospital record. Follow-up electrocardiograms at ≥ 6 months after discharge from elective vascular surgery were obtained, if available. In all, 49 patients had such follow-up electrocardiograms, and 1 demonstrated an unsuspected myocardial infarction.

Etiology of death was verified as follows: (1) in patients who died in-hospital, records were obtained, including admission diagnosis, discharge diagnosis and death certificate diagnosis; where cause of death was not clear, the medical record was reviewed by an expert observer blinded to monitoring results, and a decision was made on clinical grounds; and (2), in 1 patient who died out-of-hospital, the cause of death was confirmed by obtaining the death certificate diagnosis from the Bureau of Vital Statistics. Primary study end points included sudden and nonsudden cardiac death as defined by the Framingham criteria,¹³ and nonfatal myocardial infarction defined by: (1) unequivocal new Q waves >0.03 second in duration, or (2) ≥ 1 mm ST-segment depression in at least 1 lead when accompanied by creatine kinase level $>1.6 \mu\text{mol}\cdot\text{s}^{-1}/\text{liter}$, and MB fraction $>5\%$.¹¹ Secondary end points included noncardiac death, cerebrovascular accidents and coronary bypass surgery. Patients were coded for an end point only once, according to the following hierarchy: (1) cardiac death; (2) nonfatal myocardial infarction; (3) noncardiac death; (4) cerebrovascular accident; and (5) coronary bypass surgery.

Data and statistical analysis: For the purpose of this study, patients were considered positive for myocardial ischemia if they had ≥ 1 episode of ST-segment depression per 24 hours of monitoring. Adverse events considered included cardiac death and nonfatal myocardial infarction. Risk for an adverse event was assessed for patients with and without ischemia using univariate analysis and survival analysis. We controlled for potential confounders by using the multivariate Cox proportional-hazards model.¹⁴ Variables considered for confounding included age, gender, history of cigarette smoking of ≥ 20 pack years, hypertension (defined as diastolic blood pressure ≥ 95 mm Hg or long-term antihypertensive therapy), hypercholesterolemia (serum cholesterol ≥ 240 mg/dl or long-term therapy for hypercholesterolemia), positive family history (coronary artery disease in parents or siblings manifesting before the age of 60), diabetes (fasting serum glucose of >150

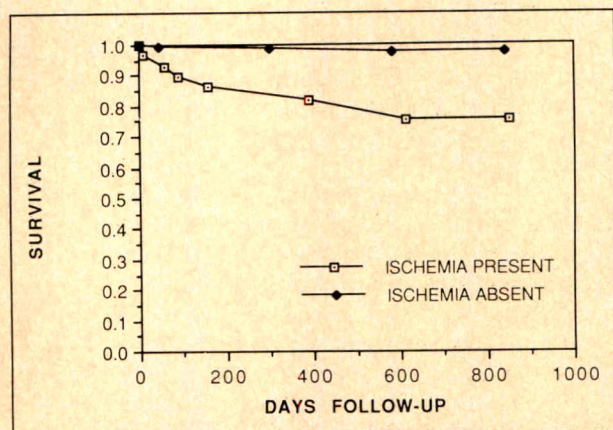


FIGURE 1. Kaplan-Meier curves demonstrating the freedom from cardiac death over time in patients with and without myocardial ischemia detected by ambulatory monitoring.

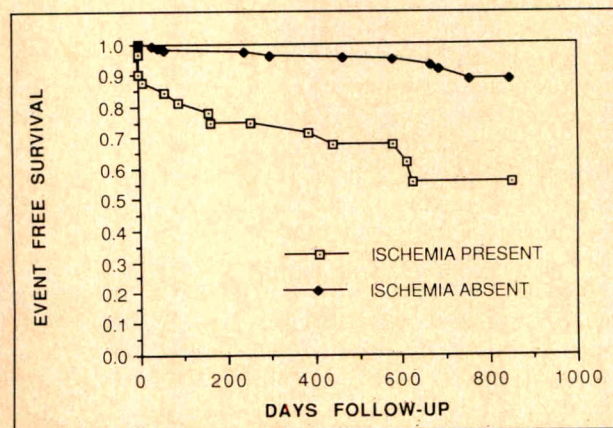


FIGURE 2. Kaplan-Meier curves demonstrating the freedom from cardiac death or myocardial infarction over time in patients with and without myocardial ischemia detected by ambulatory monitoring.

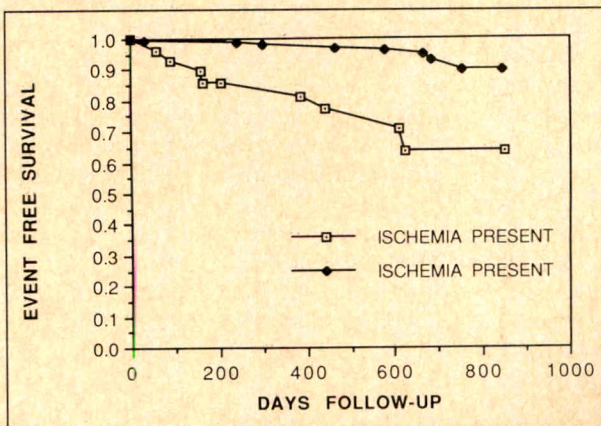


FIGURE 3. Kaplan-Meier curves demonstrating the freedom from cardiac death or myocardial infarction occurring after hospital discharge in patients with and without ischemia detected by ambulatory monitoring.

mg/dl or long-term therapy for diabetes), a history of angina pectoris (chest pain considered by the evaluating cardiologist to be unequivocal for ischemia, with or without electrocardiographic evidence of ischemia), a history of myocardial infarction or a history of coronary artery disease (defined by prior myocardial infarction, positive exercise test results, coronary bypass surgery or angina pectoris) and antianginal medications.

Study population: As previously described,¹¹ there were 124 men and 52 women, 29 to 88 years of age (mean 66). Of 176 patients, 32 (18%) had myocardial ischemia detected by monitoring. These 32 patients had a total of 75 episodes (median 2 per patient, range 1 to 9; 73 episodes [97%] were asymptomatic), lasting 1 to 720 minutes, with an average duration of 36 minutes per episode and a median of 34 minutes per patient. Ischemia was more common in patients who were aged ≥ 70 years or who had a history of hypertension, angina, myocardial infarction or coronary artery disease. Two of 3 patients who had positive exercise test results also had ischemia on monitoring.

RESULTS

Follow-up was achieved in 100% of patients. Follow-up time ranged from 1 to 850 days (mean 615, median 657) in all patients and from 67 to 850 days among those who were still alive. One hundred fifty-eight patients (90%) had follow-up interviews >1 year after monitoring, and 51 patients (29%) had follow-up >2 years after monitoring.

Adverse cardiac events: Adverse cardiac events were documented in 22 patients (Table I), including 9 cardiac deaths, 3 of which were sudden and another of which occurred in-hospital after peripheral vascular surgery. Nonfatal myocardial infarctions were documented in 13 patients who were still alive at long-term follow-up, and in an additional patient who died suddenly (and thus was coded only for cardiac death). Of these 14 myocardial infarctions, 4 were asymptomatic and diagnosed in-hospital after peripheral vascular surgery, including 1 that was diagnosed by this study's follow-up electrocardiogram but, in retrospect, occurred in-hospital on postoperative day 46 after 2 unrelated operations. Of the 9 patients who had unstable angina or ischemic pulmonary edema without myocardial infarction postoperatively while in the hospital,¹¹ 3 subsequently died because of cardiac failure, and 2 others had subsequent nonfatal myocardial infarctions. Of the patients who did not die from cardiac disease or myocardial infarctions, 9 died for noncardiac reasons, 1 had a cerebrovascular accident, and 3 had coronary artery bypass surgery.

Correlates of cardiac events: Death or infarction was more likely to occur in patients with histories of coronary artery disease (Table II). Of the 3 patients who had positive exercise test results, none died or had infarctions.

Myocardial ischemia detected by ambulatory monitoring was a significant univariate correlate of cardiac death (Figure 1) and the combined end point of cardiac death or nonfatal myocardial infarction (Figure 2). Of the 32 patients with ischemia, 6 died for cardiac reasons

(including 3 suddenly) and 6 others had myocardial infarctions (including 2 without symptoms, Table I). In contrast, of the 144 patients without ischemia, 3 had cardiac deaths and 7 others had myocardial infarctions (Tables I and II, $p < 0.0001$). None of the patients who had cerebrovascular accidents or underwent coronary bypass surgery without cardiac death or infarction and 2 of the 9 patients who had a noncardiac death had myocardial ischemia detected by ambulatory monitoring. After all confounding variables were controlled for by Cox proportional hazards analysis, myocardial ischemia remained an independent predictor of cardiac death or myocardial infarction (Table II, $p < 0.0001$). The occurrence of unstable angina or ischemic pulmonary edema in-hospital was a univariate and multivariate correlate of subsequent cardiac death and infarction after discharge (univariate risk ratio 5.5, 95% confidence interval 2.6 to 11.4), and ischemia was present in 8 of 9 such patients. Ischemia on preoperative monitoring ($p < 0.04$) and a history of myocardial infarction ($p < 0.07$) were multivariate correlates when only cardiac deaths or nonfatal myocardial infarctions occurring after hospital discharge were considered (univariate risk ratio for ischemia 4.1, 95% confidence interval 1.7 to 9.9, Figure 3). In predicting adverse cardiac outcome, the sensitivity of myocardial ischemia was 55%, the specificity was 87%, the positive predictive value was 38%, and the negative predictive value was 93%.

DISCUSSION

Our previous study demonstrated that, in a cohort of patients who presented with peripheral arterial disease for elective surgery, the presence of myocardial ischemia as detected by preoperative ambulatory monitoring added independent, incremental information toward predicting postoperative cardiac events, including death, myocardial infarction and myocardial ischemia as manifested by unstable angina or ischemic pulmonary edema.¹¹ The study excluded 98 patients who did not meet entry criteria, and these patients experienced a similar rate of postoperative cardiac events. In addition, the incidence of postoperative events was similar to that reported in other trials, suggesting no selection bias.¹¹ One limitation of our previous report was that relatively few patients had cardiac death or myocardial infarction during the postoperative period, and the majority of events were unstable angina or ischemic pulmonary edema. In the current report, additional data have demonstrated that, when the same population is followed over a longer period, preoperative myocardial ischemia continues to be an independent predictor of cardiac death and myocardial infarction. In addition, when the 9 patients who experienced postoperative unstable angina or ischemic pulmonary edema were followed for 61 to 815 days, 3 subsequently had cardiac deaths and 2 others had nonfatal myocardial infarctions. One other patient who experienced a postoperative myocardial infarction later died suddenly. While it is clear that patients who experienced postoperative cardiac events are at high risk for cardiac death and myocardial infarction on longer follow-up, preoperative myocardial ischemia on monitor-

ing is also an independent correlate of risk in those who did not experience postoperative events (Figure 3).

Our findings are consistent with those reported in preliminary long-term follow-up studies of patients with stable angina and positive exercise tests,^{5,6} in patients with a history of myocardial infarction¹ and in a cohort of asymptomatic elderly men.⁸ Our study is unique in that half of our patients had symptomatic lower extremity disease, precluding the possibility of treadmill exercise testing. Only 6 of the 23 patients who did perform exercise tests had positive tests or reached 85% of their target heart rate. The remaining patients without lower extremity disease were not exercised either because of other underlying disabilities (e.g., previous cerebrovascular accident, degenerative joint disease) or because their risk for cardiac events was felt to be sufficiently low by the evaluating cardiologist. Hence, it appears that for the majority of the patients studied, treadmill exercise testing was not an acceptable alternative for assessing risk.

Analysis of our data showed that in a multivariate proportional-hazards model, symptoms of angina pectoris (in 48 patients, 27%) and a history of coronary artery disease (in 70 patients, 40%) were not predictive factors of adverse cardiac events. This is not surprising, because most of our patients were sedentary and hence their symptoms may not be an accurate reflection of the activity of their disease. Interestingly, a significant proportion of all events preceded by ischemia detected by ambulatory monitoring (3 of 5 deaths and 3 of 6 myocardial infarctions) came with no warning symptoms, suggesting that ambulatory monitoring was the only predictor of events in these patients. Because follow-up electrocardiograms were available in only 49 patients, it is possible that the incidence of asymptomatic myocardial infarctions may be even higher in this population. However, because the physicians who cared for the patients were blinded to monitor results and because only 1 of these 49 patients had an unexpected infarction, it is unlikely that the lack of follow-up electrocardiograms in the other patients made our results biased.

Finally, the absence of myocardial ischemia during ambulatory monitoring conferred a relatively low risk

(4% at 1 year by life-table analysis) for future adverse events, regardless of a history of coronary artery disease or angina. This observation suggests that patients who have peripheral arterial disease and who do not have myocardial ischemia during ambulatory monitoring do not require additional routine screening tests. Of course, our data should not be used to argue against additional testing that would be warranted by cardiac symptoms.

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Usefulness of Tomographic Thallium-201 Imaging for Detection of Restenosis After Percutaneous Transluminal Coronary Angioplasty

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The role of tomographic thallium-201 exercise and redistribution imaging in the detection of restenosis after percutaneous transluminal coronary angioplasty (PTCA) was evaluated in 116 patients: 61 (53%) with 1- and 55 (47%) with multivessel PTCA, with a total of 185 dilated vessels. Complete revascularization was performed in 89 (77%) and partial revascularization in 27 (23%) of the patients. Restenosis was angiographically demonstrated in 69 (60%) of the patients and 85 (46%) of the vessels 6.4 \pm 3.1 months after PTCA. Disease progression in previously normal vessels was noted in 11 patients. The results were: (1) for detection of restenosis in the group of patients, single-photon emission computed tomographic (SPECT) versus exercise electrocardiographic sensitivity was 93 vs 52% ($p < 0.001$), specificity 77 vs 64%, and accuracy 86 vs 57% ($p < 0.001$). The results were similar in the complete and partial revascularization groups. (2) SPECT was 86% sensitive, specific and accurate for restenosis detection in specific vessels with comparable results for 1- versus multivessel PTCA and complete versus partial revascularization. Sensitivity, specificity and accuracy were: 89, 95 and 92% for the left anterior descending coronary artery; 88, 79 and 82% for the right coronary artery; and 76, 83 and 85% for the left circumflex coronary artery. Eighty-one percent of the diseased nondilated vessels were correctly identified. (3) Disease progression to $>50\%$ stenosis was detected with 91% sensitivity, 84% specificity and 85% accuracy. SPECT thallium-201 imaging is an excellent tool for the detection of restenosis and disease progression after PTCA in the settings of 1- and multivessel angioplasty and complete and partial revascularization.

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The evaluation of the patient after percutaneous transluminal coronary angioplasty (PTCA) has become increasingly complex. With the proliferation of angioplasty into multivessel^{1,2} and other subgroups,^{3,4} with higher rates of restenosis (40 to 50%) than the 20 to 35% rate, reported in the early era of angioplasty,⁵⁻⁸ there has been, and will continue to be, an increase in the number of patients with recurrent myocardial ischemia after PTCA. In addition, partial revascularization is increasingly being viewed as a logical approach,^{9,10} especially in elderly and high-risk patients, inevitably leaving some potential source of ischemia irrespective of restenosis. Moreover, the increasing number of patients who undergo serial angiographic evaluation will undoubtedly identify a previously underappreciated subset of patients who develop disease progression in vessels that were not significantly narrowed at the time of PTCA. The ability to detect restenosis accurately by noninvasive techniques and to differentiate it from and identify other sources of myocardial ischemia would greatly assist in the management of the patient after PTCA. In this study we evaluate the ability of single-photon emission computed tomographic (SPECT) thallium-201 exercise and redistribution imaging to accomplish these goals.

METHODS

The study group consisted of 116 consecutive patients referred for evaluation of possible restenosis who underwent SPECT imaging within a 1-week period before coronary angiography. The indication for angiographic reevaluation in 65% of the patient population was recurrent chest pain. The remainder were evaluated because of unusually complex angioplasty or positive exercise electrocardiographic or thallium-201 studies.

Exercise protocol and imaging procedure: All patients underwent standard Bruce protocol exercise testing to a symptom-limited maximum.¹¹ Standard 12-lead tracings were considered positive if there was ≥ 1 mm of horizontal or downsloping ST depression for ≥ 0.08 second after the J point compared with the resting tracing. Five patients had baseline abnormalities that precluded analysis of further ST-segment changes with exercise and were excluded from analysis of electrocardiographic restenosis detection. Three millicuries of thallium-201 were injected 1 minute before the termination of exercise. SPECT images were obtained 10

TABLE I Characteristics of Patient Population

Age (yr)	58 ± 9
Gender m/f (%)	93/23 (80/20)
Prior myocardial infarction (%)	49 (42)
Diabetes mellitus (%)	9 (8)
Antianginal drugs (%)	106 (91)
Calcium antagonists	97 (84)
Nitrates	58 (50)
β blockers	9 (8)
Chest pain before PTCA (%)	75 (65)
Chest pain after PTCA (%)	103 (89)
Mos after PTCA	6.4 ± 3.1

PTCA = percutaneous transluminal coronary angioplasty.

TABLE II Exercise Performance

Exercise duration (minutes)	7.5 ± 3.1
Maximum heart rate (beats/min)	140 ± 13
Maximum blood pressure (mm Hg)	170 ± 21
Achieved >85% of predicted maximal heart rate (%)	77 (66)
Chest pain during exercise test (%)	
Total patients	30 (26)
Patients with restenosis	39 (34)
Patients with restenosis or partial revascularization or progression, or a combination of these	36 (31)

minutes after isotope injection, 3 to 5 hours later, and, when indicated, 24 hours later, on a Siemens Orbiter large field-of-view tomographic camera interfaced with a Medical Data Systems A³ computer. We processed data using a previously described protocol.¹² Tomograms were reoriented in the short-axis, vertical long-axis and horizontal long-axis planes, reconstructed at 1 pixel/slice, representing approximately 6.2-mm thickness and divided into multiple segments for analysis. Qualitative analysis of each segment of the exercise and redistribution views was performed on a 0 to 4 scale (0 = normal, 1 = equivocally reduced thallium uptake, 2 = mildly reduced uptake, 3 = moderately reduced uptake, and 4 = severely reduced uptake) by 2 independent observers. Scores of ≥ 2 were considered abnormal and differences of opinion were resolved by consensus.

Quantitative analysis¹³ was performed and was used as an adjunct for visual analysis but final decisions were based on the visual evaluation. Myocardial ischemia was categorized as either total or partial normalization of a segment from exercise to redistribution imaging with a minimal improvement of 1 point on the visual scale.

Coronary arteriography: All patients underwent selective coronary arteriography within the week after the SPECT exercise imaging. Selective left and right coronary arteriograms were obtained with either the Judkins or Sones approach. Restenosis was defined as return of a previously dilated vessel to a $\geq 50\%$ diameter reduction, determined by magnified electronic caliper measurements.

Image correlations: The SPECT image regions were assigned to the distribution of individual vessels guided by the coronary anatomy obtained from the angiogram

TABLE III Coronary Arteriography

One-vessel PTCA (%)	61 (53)
Two-vessel PTCA (%)	40 (34)
Three-vessel PTCA (%)	15 (13)
Total vessels dilated	185
Left anterior descending	83
Right coronary	62
Left circumflex	40
Patients with restenosis (%)	70 (60)
Vessels with restenosis (%)	
Total	85 (46)
Left anterior descending	44 (53)
Right coronary	24 (39)
Left circumflex	17 (43)
Diameter reduction (%)	
Immediately before PTCA	78 ± 14
Immediately after PTCA	22 ± 6
Time of restudy	78 ± 13

PTCA = percutaneous transluminal coronary angioplasty.

recorded before the PTCA. Prediction of the absence or presence of restenosis was then made before angiographic reevaluation, based on the presence or absence of ischemic redistribution in the territory of the individual vessels. Statistical analyses were performed using the Student *t* test and chi-square analysis.

RESULTS

The characteristics of the patient population and exercise performance are listed in Tables I and II. Almost all were receiving antianginal medications. Whereas 103 (89%) of the patients experienced chest pain before angioplasty, only 75 (65%) were symptomatic at the time of restudy and only 30 (26%) experienced chest pain during the exercise test.

Coronary arteriography (Table III): The patients were evenly divided between those undergoing 1- and multivessel PTCA. Eighty-nine patients were totally revascularized (i.e., all vessels with $>50\%$ stenosis were dilated), with a total of 150 vessels undergoing PTCA. In 27 patients, only partial revascularization was accomplished, with a total of 35 vessels undergoing PTCA; 31 vessels, including 16 old total occlusions, were not dilated.

At the time of restudy, 70 (60%) of the patients had ≥ 1 vessel with restenosis. Of the total 185 vessels, restenosis occurred in 85 (46%). There were no differences in the restenosis rates in the 3 coronary arteries. In those vessels in which restenosis occurred, the percent narrowing at the time of restudy was virtually identical to that immediately before PTCA.

Development of significant disease in vessels that had $<50\%$ narrowing at the time of the angioplasty was noted in 11 patients, 9 of whom had no associated restenosis of the dilated vessels. Of the 139 vessels with $<50\%$ stenosis at the time of PTCA, significant progression did not occur in 128, whereas 11 progressed from a mean of $14 \pm 7\%$ to $76 \pm 11\%$ stenosis over an interval of 7.3 ± 3.8 months.

Exercise electrocardiography and SPECT imaging: Table IV compares the detection of restenosis in patients after PTCA by SPECT thallium-201 imaging and exercise electrocardiography. SPECT imaging was

TABLE IV Detection of Restenosis in Patients After Coronary Angioplasty: Single-Photon Emission Computed Tomographic Thallium-201 Imaging Versus Exercise Electrocardiography

	Sensitivity (%)	Specificity (%)	Accuracy (%)
All patients (n = 116)			
SPECT	93*	77	86*
Exercise electrocardiogram	52	64	57
Complete revascularization (n = 89)			
SPECT	93*	76	87*
Exercise electrocardiogram	52	64	57
Partial revascularization (n = 27)			
SPECT	93*	77	85*
Exercise electrocardiogram	50	62	56

* p < 0.001 versus exercise electrocardiogram.
SPECT = single-photon emission computed tomography.

significantly more sensitive and accurate than exercise electrocardiography in the total patient population. The specificities, although higher for SPECT imaging, were not statistically significantly different. Almost identical results were obtained in those patients undergoing complete and partial revascularization. Exercise electrocardiography was positive in 54% of the patients with disease progression.

The evaluation of restenosis in individual vessels is listed in Table V. SPECT was 86% sensitive, 86% specific and 86% accurate in the detection of restenosis in the 185 dilated vessels. There were no statistically significant differences in detection between those vessels in

TABLE V Detection of Restenosis in Individual Vessels by SPECT Thallium-201 Imaging

	No. of Vessels	Sensitivity (%)	Specificity (%)	Accuracy (%)
Total	185	86	86	86
One-vessel PTCA	61	94	79	87
Multivessel PTCA	124	81	89	85
Complete revascularization	150	86	85	85
Partial revascularization	35	86	90	89
Left anterior descending	83	89	95*	92
Right coronary	62	88	79	82
Left circumflex	40	76	83	85

* p < 0.05 left anterior descending versus right coronary.
PTCA = percutaneous transluminal coronary angioplasty; SPECT = single-photon emission computed tomography.

the 1- and multivessel subgroups. In those patients with multivessel restenosis, SPECT was 78% sensitive, detecting all restenoses in 6 of the 10 patients with 2-vessel restenosis and in the 1 patient with 3-vessel restenosis.

There were no statistically significant differences in sensitivity, specificity and accuracy in the detection of restenosis of individual vessels between the partial and total revascularization subgroups. Moreover, SPECT imaging identified 81% of the diseased, nondilated vessels. The sensitivity and accuracy were similar for the 3 major coronary arteries. The specificity for the left an-

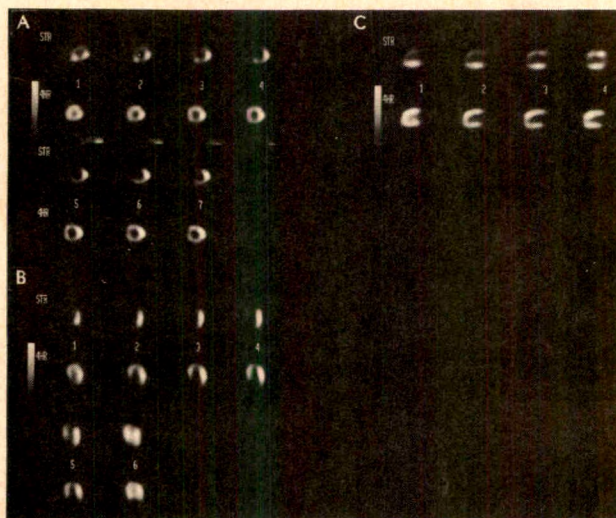


FIGURE 1. A 60-year-old man 6 months after proximal left anterior descending and distal obtuse marginal percutaneous transluminal coronary angioplasty. **A**, Short axis from apex to base (1 → 7), revealing anterior, anteroapical, inferoseptal and inferior ischemia. **B**, Horizontal long axis from superior to inferior (1 → 6), demonstrating anteroapical, inferoseptal and apical ischemia. **C**, Vertical long axis from septal to lateral (1 → 4), revealing anterior and anteroapical ischemia. Prediction: restenosis of left anterior descending coronary artery, patency of obtuse marginal. Angiography: 90% left anterior descending stenosis, patency of obtuse marginal. 4 HR = 4 hours; STR = stress.

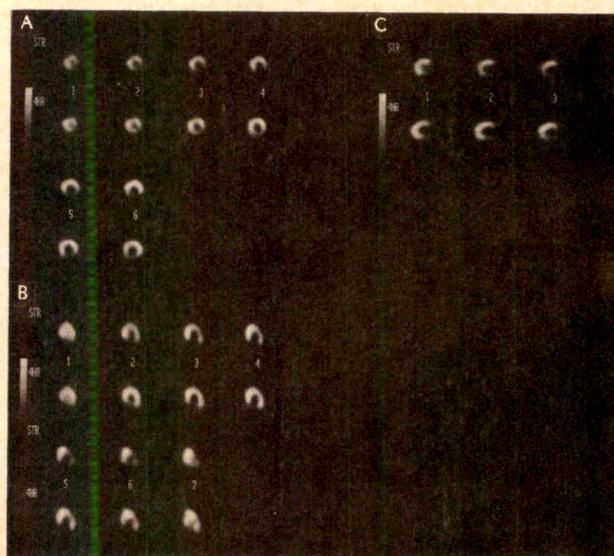


FIGURE 2. A 55-year-old man with totally occluded right coronary artery and prior 20% obtuse marginal stenosis, 3 months after proximal left anterior descending percutaneous transluminal coronary angioplasty. **A**, Short axis from apex to base (1 → 6), revealing inferior and inferolateral ischemia. **B**, Horizontal long axis from superior to inferior (1 → 7), demonstrating inferolateral ischemia. **C**, Vertical long axis from septal to lateral (1 → 3), demonstrating partially reversible inferior defect. Prediction: patency of left anterior descending coronary artery, disease progression in obtuse marginal, total right coronary artery occlusion. Angiography: patency of left anterior descending coronary artery, 80% obtuse marginal stenosis, 100% right coronary artery. Abbreviations as in Figure 1.

terior descending coronary artery was greater than for the right coronary artery but was not significantly different from that for the left circumflex coronary artery.

Disease progression in vessels with <50% stenosis at the time of the angioplasty was identified by SPECT imaging with a sensitivity of 91%, specificity of 84%, and accuracy of 85%.

Figure 1 illustrates restenosis detection in the setting of multivessel PTCA and complete revascularization and Figure 2 illustrates restenosis detection in partial revascularization and disease progression.

DISCUSSION

In this study we demonstrate the usefulness of SPECT thallium-201 imaging in the evaluation of myocardial ischemia after PTCA.

Chest pain and exercise testing: The 34% incidence of chest pain on the treadmill evaluation in the current study in patients with restenosis is similar to the 40% reported by Bengtson et al¹⁴ in patients with restenosis and to the 25%¹² and 30%¹⁴ previously reported in patients with coronary artery disease in general. While the high percentage of patients taking antianginal medications at the time of exercise testing may have contributed to the low incidence of angina, it clearly did not affect the sensitivity of SPECT imaging. Thus, exercise-induced angina is an insensitive marker for restenosis. The incidence of chest pain was not higher in patients with disease progression or partial revascularization plus restenosis despite the greater number of diseased vessels, again highlighting the lack of usefulness of exercise-induced chest pain as a marker for ischemia.

Exercise electrocardiography: This study also confirms the insensitivity of exercise electrocardiography in the detection of restenosis. The sensitivity of 52%, while higher than the 34%¹⁴ and 24%¹⁵ of prior reports, is far from acceptable as a diagnostic tool. It should be emphasized that all patients underwent *maximal* exercise testing despite only 66% achieving $\geq 85\%$ of the predicted maximal heart rate. While the high percentage of patients using antianginal medications may again be cited to explain the poor sensitivity, it was not a significant factor for SPECT imaging. Moreover, it may be neither safe nor realistic to discontinue medications in an attempt to improve sensitivity.

The results for exercise electrocardiography were virtually identical in the partial and complete revascularization groups despite the expected higher incidence of positive studies in the partial revascularization group, which by definition had an additional potential source for myocardial ischemia (i.e., the nondilated vessel). In addition, the usefulness of exercise electrocardiography in the partial revascularization group is questionable because a positive response may result from either restenotic or nonrevascularized areas. Similarly, even in patients with complete revascularization, a positive electrocardiographic response may be indicative of disease progression rather than restenosis.

SPECT imaging: There are no prior reports of restenosis detection by either planar or SPECT thallium-201 imaging, although prediction of future restenosis by planar

thallium imaging performed within the first month of PTCA has been evaluated.^{16,17} Exercise radionuclide ventriculography was noted to have an accuracy of 77% for restenosis detection in patients.¹⁸ However, this technique has not been found to be reliable in identifying disease in individual arteries. Moreover, an abnormal response would be expected in patients with partial revascularization independent of restenosis.

SPECT thallium-201 imaging, by virtue of its ability to identify disease in individual vessels, is ideally suited for the evaluation of myocardial ischemia after PTCA, with results far superior to those for exercise electrocardiography. We demonstrate its usefulness in detecting restenosis with comparable results after both 1- and multivessel PTCA and complete or partial revascularization in the current study.

Prior studies have documented the detection of disease in individual vessels and patients by SPECT thallium-201 imaging with visual or quantitative analysis, or both, in a general coronary artery disease population in patients who have not undergone PTCA.¹⁹⁻²¹ For detection of disease in groups of patients, sensitivities ranged from 87 to 97%, specificities from 68 to 87%, and accuracies from 84 to 87%. These results are comparable to the 93% sensitivity, 77% specificity, and 86% accuracy in the current study in a PTCA setting, using visual SPECT analysis. For the localization of disease to specific vessels, the 86% sensitivity, 86% specificity, and 86% accuracy of this study are slightly superior to the prior reports in a non-PTCA setting. The most likely explanation for this superiority lies in the method of image correlation, whereby image regions were assigned to the distribution of individual vessels guided by the coronary anatomy obtained from the angiogram recorded before the angioplasty. Thus, the coronary dominance and exact distribution of all vessels were known at the time of the SPECT analysis, an advantage not shared by studies evaluating patients without prior angiography.

Partial revascularization and disease progression:

Whereas SPECT thallium-201 imaging has been used to evaluate residual ischemia within 1 month of 1-vessel PTCA in patients with multivessel disease,⁹ there are no prior reports concerning restenosis detection in patients who have undergone partial revascularization. The similar results in the partial and complete revascularization groups provide a rational basis for the use of SPECT thallium-201 imaging in both settings. Inasmuch as there are no clinical or electrocardiographic criteria for the differentiation of myocardial ischemia resulting from a restenotic dilated vessel from that secondary to a diseased and nondilated artery, SPECT imaging may play a unique role in the partial revascularization group.

Disease progression in previously normal nondilated arteries, described in angiographic evaluations^{22,23} but not previously evaluated by SPECT thallium-201 imaging, poses a similar problem by providing an alternative source of ischemia. SPECT imaging was equally reliable in the identification of vessels affected by disease progression and restenosis and thus may be used to evaluate both sources of ischemia.

Clinical implications: The increasing application of PTCA to subgroups with a 40 to 50% prevalence of restenosis provides the ideal setting for an accurate diagnostic tool that can, by Bayes' theorem,²⁴ yield the greatest change from pretest to posttest likelihood of restenosis. The high degree of accuracy reported in the current study presents evidence for the ability of SPECT thallium-201 imaging to fulfill this need. In addition to identifying the patient with restenosis, SPECT imaging, by virtue of identifying the restenotic vessel and the amount of ischemic myocardium, may be used to assist in determining the need for angiographic reevaluation.

The comparably high accuracies in the numerous potential settings of angioplasty (i.e., 1- and multivessel, partial and complete revascularization and disease progression), confer on SPECT imaging the prerequisite qualities for evaluating patients in an era of progressively more complex PTCA. We therefore recommend that SPECT thallium-201 exercise and redistribution imaging become an integral part of the evaluation of myocardial ischemia in the period after PTCA.

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Coronary Artery Disease in the Octogenarian: Angiographic Spectrum and Suitability for Revascularization

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The angiographic findings of 84 consecutive octogenarians presenting with symptoms of coronary artery disease (CAD) were examined to determine the extent of CAD as well as suitability for both coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA). The frequency of 0-, 1-, 2-, and 3-vessel and left main CAD was 7, 14, 21, 57 and 13%, respectively. Based on angiographic criteria, 69 of 78 patients (88%) with significant CAD had suitable coronary anatomy for CABG. Only 24 patients (31%) had coronary anatomy amenable to PTCA. CABG was performed in 19 patients with an operative mortality of 16% and major complication rate of 37%. PTCA was performed in 12 patients with a clinical success rate of 83%, mortality of 8% and major complication rate of 8%. It is concluded that in octogenarians with CAD, cardiac catheterization will often reveal coronary anatomy that is suitable for CABG but less suitable for PTCA. The morbidity and mortality associated with these interventions are high.

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Age is an important determinant of the risk of developing coronary artery disease (CAD).¹⁻³ Consequently, as the population ages, increasing numbers of elderly patients are presenting with symptoms of angina and myocardial infarction. Frequently, these patients are referred for cardiac catheterization in an effort to identify coronary lesions that may be amenable to revascularization. Recent data have suggested that in the elderly coronary artery bypass grafting (CABG) may be associated with a higher morbidity and mortality than similar procedures performed in younger patients.⁴⁻⁷ Octogenarians form a unique subgroup of the elderly in whom this risk may be even greater.⁸⁻¹² With the expanded use of percutaneous transluminal coronary angioplasty (PTCA), revascularization may be performed more safely and effectively in older patients.^{13,14} The spectrum of CAD in octogenarians as well as the suitability for either CABG or PTCA remains to be determined. We therefore examined the angiographic findings as well as the feasibility and results of revascularization in patients aged ≥ 80 years with symptoms of CAD referred for cardiac catheterization.

METHODS

We reviewed the catheterization reports of 119 consecutive patients aged ≥ 80 years who underwent diagnostic coronary arteriography at our institution between 1983 and 1987. The study group consisted of 84 patients who were referred for cardiac catheterization for symptoms of CAD. Patients were excluded if their predominant symptom was thought to be secondary to valvular heart disease or if they had previously undergone either CABG or PTCA. Presenting symptoms (New York Heart Association class) as well as medication history, cardiac risk factor profile, and concomitant medical illness were obtained by review of the patient's medical records and catheterization reports.

Systemic hypertension was defined as a systolic blood pressure >160 mm Hg systolic or 95 mm Hg diastolic or a history of hypertension that was being treated with medication at the time of catheterization. Hypercholesterolemia was defined as a fasting serum cholesterol ≥ 260 mg/dl. Patients who were being treated with either diet, insulin or oral hypoglycemic agents were classified as having diabetes mellitus. Family history of premature CAD in first-degree blood relatives (before age 65) was noted as was history of current or previous cigarette usage. Renal insufficiency was defined as a serum creatinine >1.5 mg/dl on admission laboratory

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TABLE I Patient Characteristics

	No. of Pts. (n = 84)
Age (yrs)	82 ± 2.4
Age range (yrs)	80–90
Gender	
Men	40 (48%)
Women	44 (52%)
Reason for catheterization	
Postinfarction angina	33 (39%)
Unstable angina	23 (27%)
Stable angina	25 (30%)
Other	3 (4%)
Associated medical conditions	
Chronic obstructive pulmonary disease	3 (4%)
Renal insufficiency	4 (5%)
Prior cerebral vascular events	12 (14%)
Peripheral vascular disease	6 (7%)
Prior myocardial infarction	45 (54%)

evaluation. Patients with previous stroke, transient ischemic attack or carotid endarterectomy were classified as having prior cerebral vascular events and those with intermittent claudication, documented abdominal aortic aneurysm or previous peripheral vascular surgery were assumed to have peripheral vascular disease. History of chronic obstructive pulmonary disease was noted.

Coronary arteriography was performed by either the Sones or Judkins technique. The degree of coronary luminal narrowing was determined visually and represents a consensus opinion of 2 experienced angiographers (GJK, SML). A significant stenosis was considered to be present if a $\geq 70\%$ reduction in internal luminal diameter was presented in a major epicardial segment of the left anterior descending, left circumflex, or right coronary artery, or if $\geq 50\%$ obstruction was present in the left main coronary artery. When multiple significant narrowings were present in the same artery, the narrowing of the greatest severity was said to account for that artery's stenosis.

Evaluation of the extent of CAD was performed by examining the number of major segments of the arterial tree determined to have a significant stenosis. In the presence of a right or balanced circulation, the segments considered were the left anterior descending, left circumflex and right coronary arteries. In the case of a left dominant circulation, the 3 segments evaluated were the left anterior descending, the proximal left circumflex and its marginal system, and the distal left circumflex and its posterolateral branches. Left ventriculography was performed in the 30° right anterior oblique projection with left ventricular ejection fraction being calculated by the area-length method.¹⁵ The degree of mitral regurgitation was graded by visual estimation and was recorded on a scale of 1 to 4+. The severity of aortic stenosis was calculated by the Gorlin formula.¹⁶ Significant valvular disease was said to be present if the severity of mitral regurgitation was $>2+$ or if the aortic valve area calculated to be ≤ 1.0 cm².

The suitability of patients for either CABG or PTCA was based only on angiographic findings and did not take into consideration concomitant medical disease. Consideration was given to the number, location and

morphology of significant coronary narrowings. Patients with a significant stenosis in the left main coronary artery were not considered PTCA candidates as were patients with diffuse narrowings, totally occluded arteries, narrowings involving major branch points of an artery, or narrowings located on significant bends in an artery. Those with multivessel CAD were considered as PTCA candidates if all lesions were amenable to balloon catheter dilatation or if a culprit lesion could be identified based on clinical presentation, electrocardiographic findings and angiographic appearance of the vessel. Sequential stenoses were not an exclusion criterion for angioplasty if each stenosis was judged suitable for dilatation. Based on the number of significant stenoses that were amenable to PTCA, patients were classified as being angioplasty candidates with the potential for either complete or incomplete revascularization.

Patients were considered candidates for CABG if each vessel with a significant stenosis was free of atherosclerotic disease in its distal portion and of adequate size in order to accept a bypass graft. Concurrent left ventricular dysfunction (ejection fraction $<30\%$) was not considered an exclusion criterion for surgery; however, patients with left ventricular dysfunction combined with significant valvular disease were considered ineligible for CABG. Patients who were not candidates for either CABG or PTCA were grouped as medical treatment. Final disposition for each patient as well as outcome of revascularization procedures when performed was obtained by medical record review.

RESULTS

The presenting symptoms, clinical characteristics and concurrent medical conditions for the 84 patients are listed in Table I. The mean age was 82 years (range 80 to 90). In most of the patients, cardiac catheterization was performed for postinfarction, unstable or severe angina. Two patients underwent catheterization for recurrent postmyocardial infarction pulmonary edema thought to be secondary to myocardial ischemia. One patient underwent arteriography as part of a preoperative assessment before aortic aneurysm resection after an anterior myocardial infarction. Eighty patients (95%) were receiving long-acting nitrates, 36 patients (43%) were being treated with β blockers, and 71 patients (85%) were receiving calcium antagonists. Seventy-three patients (87%) were receiving combination antianginal therapy at the time of catheterization.

Forty-five patients (53%) were hypertensive, 33 patients (39%) were either current or prior cigarette smokers, 21 patients (25%) had diabetes mellitus, 14 patients (17%) reported a positive family history of premature CAD, and 6 patients (7%) were hypercholesterolemic. Examination of cardiac risk factor combinations was notable for 12 patients (14%) with no risk factors, 36 patients (43%) with 1 cardiac risk factor, 26 patients (31%) with 2 risk factors, 9 patients (11%) with 3 risk factors, and 1 patient (1%) with 4 risk factors. No patient had all 5 major cardiac risk factors.

Six of the 84 patients (7%) who underwent catheterization were without significant CAD. Significant 1-vessel CAD was present in 12 patients (14%), 2-vessel

CAD in 18 patients (22%), and 3-vessel CAD in 48 patients (57%). Significant narrowings in the left main coronary artery were present in 11 patients (13%). All patients with significant left main coronary stenoses also had concomitant right CAD and were therefore classified as having 3-vessel CAD. Significant aortic stenosis was present in 2 patients and significant mitral regurgitation was present in 5 patients. All patients with significant valvular disease also had significant CAD. Ventriculography was performed in 53 patients. Mean ejection fraction was 51% (range 22 to 81%). Eight patients (15%) had a left ventricular ejection fraction <30%, 20 patients (38%) had an ejection fraction between 30 and 49%, and in 25 patients (47%) the ejection fraction was \geq 50%. Five patients (6%) experienced complications resulting from cardiac catheterization (2 transient neurologic deficits, 1 acute renal failure, 1 peripheral vascular compromise and 1 procedural related death).

Based on angiographic criteria, the suitability for CABG or PTCA was determined in the 78 patients with significant coronary obstructions (Table II). Sixty-nine patients (88%) were judged to have suitable anatomy for CABG, whereas only 24 patients (31%) were considered to have suitable anatomy for PTCA. Seven patients were judged not to have suitable anatomy for either CABG or PTCA. One additional patient was excluded as a bypass candidate due to a combination of left ventricular dysfunction and severe mitral regurgitation. Of the 24 patients (31%) considered candidates for coronary angioplasty, 16 patients had the potential for complete revascularization by PTCA. The remaining 8 patients were considered angioplasty candidates with the potential for incomplete revascularization. One patient was considered to be a candidate for PTCA but not CABG because of a focal stenosis in a small circumflex marginal branch. All other patients considered candidates for angioplasty were also considered CABG candidates. By angiographic criteria, a total of 70 patients (90%) were considered candidates for revascularization by either CABG or PTCA.

CABG or PTCA was performed in 31 of 70 patients (44%) whose coronary anatomy was judged suitable for

TABLE III Studies Examining Cardiac Surgery and Coronary Angioplasty in Octogenarians

First Author	Year	No. of Pts.	Procedure	Morbidity (%)	Mortality (%)
Rich ⁸	1985	25	CABG/valve/both*	92 [†]	4
Tsai ⁹	1986	76	CABG/valve/both	29	13
Naunheim ¹⁰	1987	23	CABG \pm valve [‡]	50	22
Edmunds ¹¹	1988	100	CABG/valve/both/other*	28	29
Kern ²⁹	1988	21	PTCA	38	19

* Includes left ventricular aneurysmectomy, ventricular septal defect repair, left atrial tumor resection or ascending aortic aneurysm repair.

[†] Postoperative arrhythmias included as morbidity.

[‡] One patient received CABG and ventricular septal defect repair.

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; Valve = mitral valve replacement or valvuloplasty, aortic valve replacement, or mitral replacement or valvuloplasty and aortic valve replacement.

revascularization (Figure 1). Twelve of 24 angioplasty candidates underwent PTCA. Six of these patients had 1-vessel, 2 patients had 2-vessel and 4 patients had 3-vessel CAD. Three patients with 3-vessel and 1 patient with 2-vessel CAD had complete revascularization by angioplasty. The remaining 8 patients had complete revascularization by PTCA. PTCA was attempted in 17 narrowings in 15 arteries. Initial angiographic success (<50% residual stenosis after PTCA) was achieved in 15 lesions attempted (88%). Initial clinical success (successful dilatation of all lesions attempted in each patient) was achieved in 10 patients (83%). One patient died from cardiogenic shock after unsuccessful angioplasty of a left anterior descending artery stenosis. One additional patient undergoing successful PTCA had a laceration of the femoral artery requiring surgical repair.

Nineteen of 69 patients (28%) deemed bypass candidates underwent CABG. One patient with 1-vessel CAD and unstable angina underwent CABG and mitral valve replacement. Two patients with 2-vessel and 16 patients with 3-vessel CAD underwent CABG including 4 patients with significant stenoses in the left main coronary artery. Three patients (16%) died after operation and 7 additional patients (37%) had major

FIGURE 1. Potential treatment options, treatment received and discharge status of the 78 octogenarians with significant coronary artery disease (CAD). CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

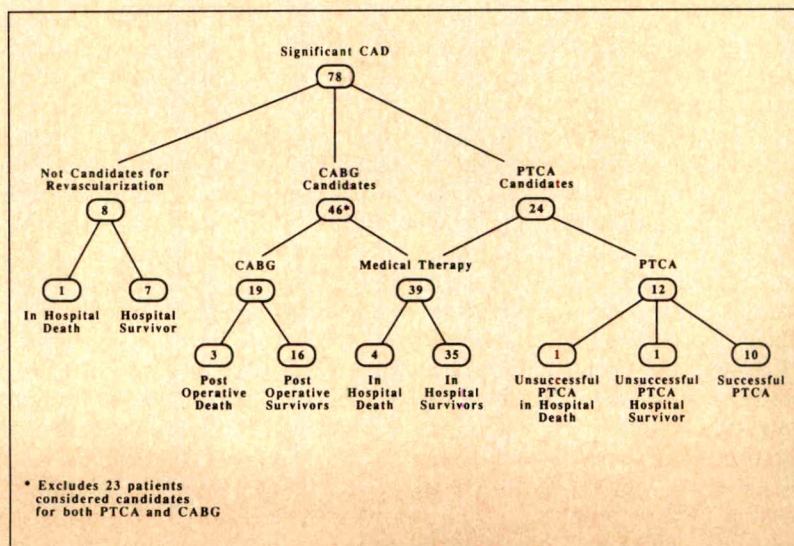


TABLE II Angiographic Suitability for Either CABG or PTCA for the 78 Patients with Significant Coronary Narrowings

No. of Coronary Arteries Severely Narrowed	No. of Pts.	PTCA Candidates		CABG Candidates
		Complete* Revascularization	Incomplete* Revascularization	
1	12	11 (92%)	—	11 (92%)
2	18	4 (22%)	4 (22%)	15 (83%)
3	37	1 (3%)	4 (11%)	32 (86%)
Left main	11	—	—	11 (100%)
Total	78	16 (21%)	8 (10%)	69 (88%)

* Complete and incomplete refer to the extent of revascularization potentially achievable with coronary angioplasty.
CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

postoperative complications (2 myocardial infarctions, 1 mediastinitis, 1 pneumonia, 1 ulnar palsy, 1 femoral thrombosis and 1 gastrointestinal hemorrhage).

Thirty-nine patients whose coronary anatomy was judged suitable for the procedure did not achieve revascularization. Thirty-five of these patients continued with medical therapy, were stabilized and discharged alive (including 2 patients who were offered revascularization but refused [1 PTCA, 1 CABG]). Four additional patients died of cardiac events during initial hospitalization including 1 catheterization-related death. Of the 8 patients whose coronary anatomy was judged not amenable to revascularization, 7 were stabilized medically and discharged alive with 1 additional patient dying after an in-hospital myocardial infarction.

DISCUSSION

Although coronary revascularization has been performed in selected octogenarians, the percentage of such patients presenting with angina who are candidates for these procedures has not been previously demonstrated. Additionally, the spectrum of CAD in this population needs to be defined. In general, coronary angiographic findings examining patients with chronic stable angina, unstable angina and postmyocardial infarction have revealed a similar incidence of left main and multivessel CAD.¹⁷ These reports, however, have been skewed toward younger persons or limited to older patients who have been preselected as candidates for revascularization.

The 7% incidence of normal or near-normal coronary arteries found in our study is comparable to the 2 to 19% incidence described in younger patients with severe or unstable angina.¹⁸⁻²⁰ In contrast, our finding of a 13% incidence of left main and 57% incidence of 3-vessel CAD approaches the upper limits of what is reported in these series. The impact of advancing age on the extent of CAD has previously been described. Comparison of the Coronary Artery Surgery Study registry patients ≥ 65 years old with those < 65 years old was remarkable for older patients having a significantly greater incidence of both left main (13 vs 9%) and 3-vessel CAD (61 vs 46%).²¹ Moreover, among men and women with definite or probable angina, the likelihood

of having significant multivessel CAD increases progressively with advancing age.²

The severity of CAD found in the octogenarians we studied was not accompanied by a high incidence of cardiovascular risk factors. Forty-eight patients (57%) had either no or only 1 risk factor for CAD. In younger persons, risk factors are important predictors of groups at high risk for the later occurrence of angina, myocardial infarction and cardiac death.^{3,22} As subjects age, risk factors lose their predictive powers. Advanced age has been shown to be such a potent risk factor for CAD development that its presence attenuates the effect of other clinical variables.^{1,23}

In addition to older persons having more extensive CAD, they may also be prone to develop diffuse atherosclerosis resulting in fewer patients being candidates for CABG. This was not the case in octogenarians we studied. Sixty-nine patients (88%) with significant CAD were judged acceptable surgical candidates based on angiographic criteria. Previous studies examining younger patients with unstable angina have reported similar surgical candidacy rates ranging from 82 to 91%.^{19,20,24} Thus, even though advanced age is accompanied by a higher number of diseased vessels, the potential for these vessels to be amenable to bypass grafting remains excellent.

In the last decade the age limit for CABG has been increasing.^{25,26} Bypass procedures in the elderly can be expected to offer improvement in anginal symptoms and may prolong survival in selected subsets.²⁷ These procedures are associated with an increase in operative risk. In our study, an operative mortality of 16% and major morbidity of 37% was found in patients undergoing CABG. Recent reports examining the role of cardiac surgery in octogenarians have demonstrated similar findings.⁸⁻¹¹ Perioperative mortality in these series have ranged from 4 to 29%, with complications occurring in 29 to 92% of surgical survivors (Table III).

Because of the high surgical morbidity and mortality reported, PTCA has been suggested as a therapeutic alternative in the severely symptomatic elderly patient. Although early studies have found advanced age to have an adverse effect on the initial success rate of PTCA,²⁸ more recent data indicate that angioplasty can be performed in the elderly with a primary success rate comparable to results observed in younger groups.^{13,14} Reported experience with PTCA in the octogenarian is scant. In our study, angiographic success was achieved in 87% of vessels attempted, with a clinical success rate of 83%. Procedure-related mortality occurred in 8% of patients, with an additional 8% experiencing a major complication. In a prior study, Kern et al²⁹ evaluated coronary angioplasty in the octogenarian. Thirty-two stenoses were attempted in 21 patients, with an initial angiographic success rate of 78% and a clinical success rate of 67%. Four patients (19%) died as a result of either complications from angioplasty or emergency CABG required after failed PTCA. An additional 8 patients (38%) had major complications.

In contrast to the high angiographic candidacy rate for CABG, only 24 octogenarians (31%) were judged

acceptable candidates for angioplasty. Leeman et al²⁴ evaluated the feasibility of PTCA in 92 patients with unstable angina (mean age 61 years).²⁴ Based on angiographic findings, Leeman observed that PTCA was possible in 66% of patients. The lower candidacy rate for angioplasty noted in our patients most probably is explained by their higher incidence of both left main and multivessel CAD. In contrast to the 62% incidence of left main or multivessel CAD reported by Leeman, 79% of the octogenarians in our study had these same lesions. As the number of diseased vessels increases, both the candidacy for PTCA and the ability to achieve complete revascularization with PTCA is reduced.³⁰

There are several limitations to our study. An inherent referral bias may have been present because octogenarians judged in otherwise good health may have been selected for angiography. Additionally, angiograms were reviewed retrospectively without knowledge of the general medical condition of the patient. In this elderly group of persons, both angiographic and clinical factors need to be considered in selecting patients as potential candidates for revascularization. Some patients considered to be candidates for CABG or PTCA based on angiographic findings may have been excluded from one or both of these procedures because of concomitant non-cardiac disease. Finally, the selection of patients as candidates for either CABG or PTCA may vary with the clinical judgment of individual physicians.

Conclusion: Multivessel CAD is frequently found in octogenarians with severe or unstable angina. Angiography will more often reveal coronary anatomy that is suitable for CABG but less often suitable for PTCA. However, the in-hospital morbidity and mortality associated with revascularization procedures in this patient group is high.

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Prevalence and Correlates of Increased Lung/Heart Ratio of Thallium-201 During Dipyridamole Stress Imaging for Suspected Coronary Artery Disease

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There is little information concerning the prevalence and clinical correlates of increased pulmonary thallium-201 uptake during dipyridamole thallium-201 stress imaging. Accordingly, the clinical characteristics and quantitative thallium-201 findings were correlated with quantitative lung/heart thallium-201 ratio in 87 patients undergoing dipyridamole thallium-201 stress testing. Nineteen patients (22%) had an elevated ratio (>0.51). These patients were more likely to have had an infarction, to be taking β blockers, and have a lower rate-pressure product after dipyridamole administration than those with a normal ratio ($p < 0.03$). An elevated ratio was associated with a greater likelihood of initial, redistribution and persistent defects, as well as left ventricular cavity dilatation on thallium-201 imaging ($p < 0.05$). In addition, the number of myocardial segments demonstrating initial, redistribution and persistent defects was also greater in patients with increased ratios ($p < 0.03$). Multivariate analysis demonstrated that the presence of redistribution and left ventricular cavity dilatation were the most significant correlates of lung/heart thallium-201 ratio.

It is concluded that the prevalence of increased lung/heart thallium-201 ratio with dipyridamole thallium-201 stress imaging is similar to that seen with exercise stress imaging. As with exercise thallium-201 imaging, increased pulmonary thallium-201 uptake may be a marker of functionally more significant coronary artery disease.

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The mechanism(s) and significance of increased lung uptake of thallium-201 during exercise stress imaging have been investigated in detail.¹⁻¹⁰ Postulated to reflect pulmonary edema secondary to transient global left ventricular dysfunction,^{2,6} this finding during exercise stress has been demonstrated to have major prognostic implications. The presence of this finding identifies a subgroup of patients at higher risk for subsequent cardiac events.⁷⁻¹⁰ In patients unable to exercise, thallium-201 imaging after intravenous injection of dipyridamole is an alternative approach for the detection of coronary artery disease¹¹⁻¹⁴ and risk stratification.¹⁵⁻¹⁹ There is scant information concerning the prevalence and significance of increased lung/heart ratio during dipyridamole thallium-201 imaging. The goals of this study, therefore, were to determine the prevalence and correlates of increased pulmonary uptake of thallium-201 with dipyridamole stress imaging and to compare the prevalence of this finding to that in a comparable group of patients undergoing exercise stress imaging.

METHODS

Patient group: The study group comprised 87 consecutive patients referred to the University of Virginia Hospital for dipyridamole thallium-201 stress imaging for suspected coronary artery disease. There were 51 men and 36 women, aged 34 to 75 years (mean \pm standard deviation, 61 ± 9). The criteria for exclusion included age >75 years, decompensated heart failure, unstable angina, myocardial infarction within the antecedent 6 months, bronchospastic disease and chronic aminophylline use. No changes were made in the medications before the test. Pertinent cardiac and noncardiac variables, left ventricular hypertrophy on the electrocardiogram, coronary risk factors and concurrent drug therapy were noted. A cohort of 255 patients was also identified who underwent exercise stress thallium-201 imaging during the same period.

Imaging protocol: The dipyridamole thallium-201 imaging protocol used in our laboratory has been previously described.¹² Dipyridamole (0.56 mg/kg) was administered intravenously over the course of 4 minutes with patients in the supine position, followed 3 minutes later by an injection of 2.0 mCi of thallium-201. From the initiation of dipyridamole infusion, blood pressure

and a 12-lead electrocardiogram were recorded every minute for the first 10 minutes, every 2 minutes for the next 10 minutes and every 5 minutes for the final 25 minutes. The occurrence of chest pain was recorded. The exercise protocol used in our laboratory has also been previously described.⁷ For both protocols, initial imaging commenced 10 minutes after thallium-201 injection in the anterior projection, followed by the 45° and 70° left anterior oblique projections. This same sequence was repeated 2 to 3 hours later.

Quantitative image analysis: Myocardial thallium-201 activity was assessed using a previously described computer-assisted approach.²⁰ After background subtraction, thallium-201 activity was measured in 11 segments in 3 views. The initial images were assessed by 2 independent observers for the presence or absence of defects based on quantitative criteria previously established in our laboratory.²⁰ The delayed images were assessed for the presence of redistribution. An abnormal study was defined as one exhibiting ≥ 1 defect. Differences in interpretation were resolved by a third observer.

Lung thallium-201 uptake was measured over the midleft lung field in the anterior view before background subtraction and after image smoothing (Figure 1). The lung/heart thallium-201 ratio was expressed as the ratio of the counts from the 7×7 pixel regions in the lung and the myocardium demonstrating the highest count activity. The thallium-201 imaging variables analyzed for this study included the number of segments with initial, redistribution and persistent defects, and left ventricular cavity dilatation.

Statistical analysis: Data were expressed as either mean ± 1 standard deviation or as proportions. The lung/heart ratio was considered normal if it was <0.51 , and increased if it was >0.51 .⁶ Univariate analysis of continuous variables were compared in patients with

and without an increased ratio by the Student's *t* test. The Fisher exact test was used to compare differences in proportions. For multivariate analysis, multiple stepwise linear regression with the lung/heart ratio as the dependent variable was used. Twenty-four clinical and thallium-201 variables were correlated with the lung/heart ratio.

RESULTS

Figure 2 illustrates data from 2 of the patients. Figure 2A shows the initial unprocessed images in the anterior view in a patient in whom the lung/heart ratio is not elevated. Myocardial uptake and washout of thallium-201 in this particular patient were normal. In contrast, an increased lung/heart ratio was evident (Figure 2B). Multiple segments exhibited initial defects and redistribution in this patient.

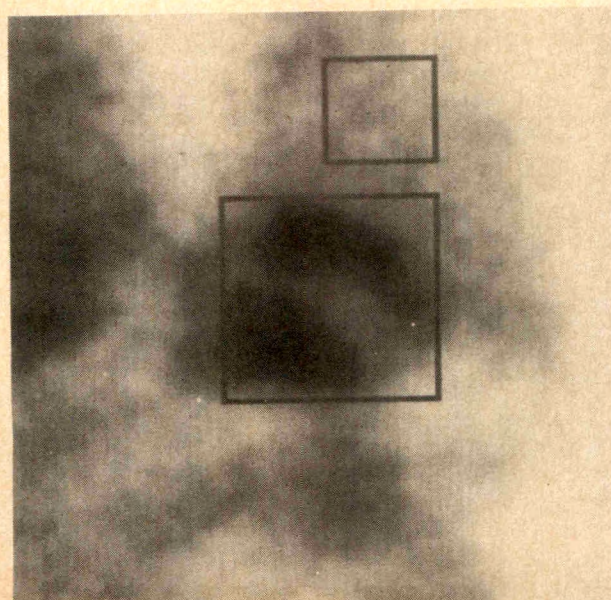


FIGURE 1. The method for quantitating the lung/heart thallium-201 ratio. See text for details.

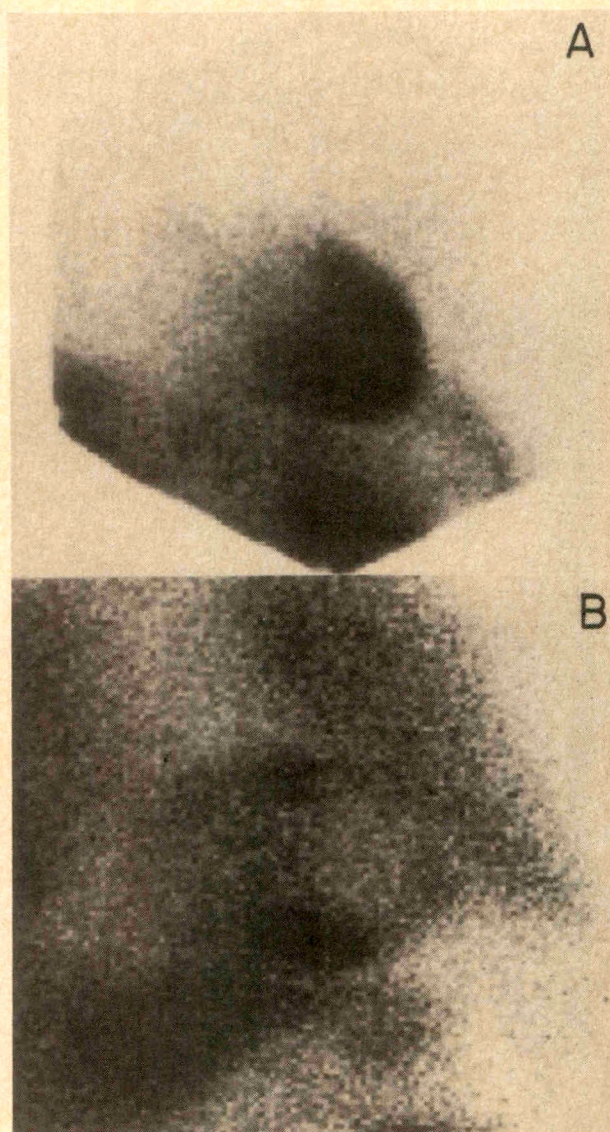


FIGURE 2. A, anterior view from a patient with normal lung and myocardial activity after dipyridamole infusion; B, similar view from a patient with markedly increased lung activity who also demonstrated multiple segments showing initial defects and redistribution.

TABLE I Clinical Correlates of Increased Lung/Heart Thallium-201 Ratio

Variable	N Ratio (≤ 0.51) (n = 68)	↑ Ratio (> 0.51) (n = 19)	p Value
Age (yr)	61 \pm 10	62 \pm 8	0.70
Male (%)	37 (55)	14 (74)	0.19
History of			
Heart failure (%)	12 (18)	4 (21)	0.74
Myocardial infarction (%)	23 (34)	14 (74)	0.01*
Hypertension (%)	46 (68)	9 (47)	0.12
Valvular disease (%)	4 (6)	0 (0)	0.57
Revascularization (%)	15 (22)	3 (16)	0.75
Diabetes mellitus (%)	20 (29)	6 (32)	0.99
Smoking (%)	38 (56)	13 (68)	0.43
β blocker (%)	14 (21)	9 (47)	0.04*
Calcium blocker (%)	30 (44)	6 (32)	0.59
Digoxin (%)	11 (16)	1 (5)	0.45
ACE inhibitor (%)	10 (15)	2 (11)	0.99
Left ventricular hypertrophy (%)	9 (13)	2 (11)	0.99
During dipyridamole test:			
Chest pain (%)	23 (34)	4 (21)	0.40
ST depression (%)	6 (9)	2 (11)	0.99
RP product ($\times 10^3$)	11.4 \pm 2.9	9.7 \pm 2.1	0.02*

* Significantly different between the 2 groups.

ACE = angiotensin-converting enzyme; N = normal; RP = rate pressure.

Nineteen of the 87 patients undergoing dipyridamole stress (22%) had increased lung/heart thallium-201 ratio compared with 35 (14%) of the 255 undergoing exercise stress testing (difference not significant). The lung/heart ratios for patients with normal and abnormal dipyridamole stress images (0.41 ± 0.05 and 0.48 ± 0.08 , respectively, $p < 0.001$) were similar to those for normal and abnormal exercise images (0.39 ± 0.06 and 0.46 ± 0.09 , respectively, $p < 0.001$).

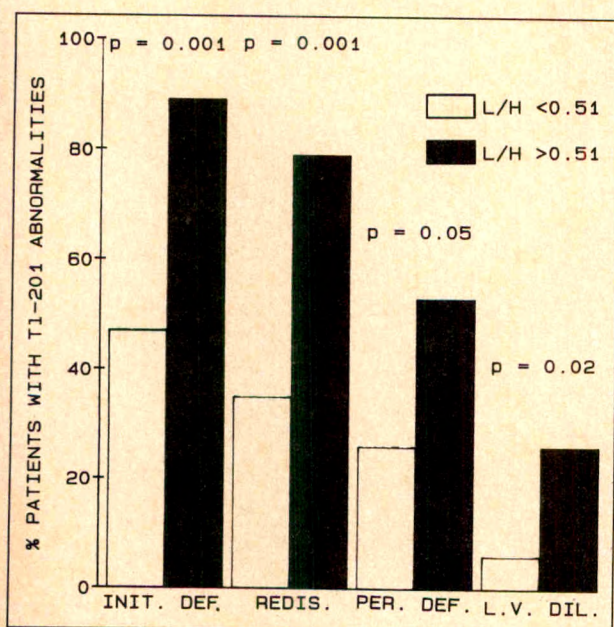


FIGURE 3. The incidence of various abnormalities on thallium-201 imaging (TI-201) in patients with and without increased lung/heart (L/H) thallium-201 ratio. INIT. DEF. = initial defects; L.V. DIL. = left ventricular dilatation; PER. DEF. = persistent defects; REDIS. = redistribution.

Clinical correlates of increased lung/heart ratio:

Table I depicts pertinent clinical characteristics in patients with and without increased lung/heart thallium-201 ratios on the dipyridamole stress images. There were no differences between the 2 groups with respect to age, gender, presence of risk factors such as smoking, hypertension and diabetes mellitus, presence of significant valvular disease, or electrocardiographic evidence of left ventricular hypertrophy. Those with increased lung/heart ratios, however, were more likely to have had an infarction and to be taking β -blocker therapy. The incidence of chest pain or ST-segment depression and the magnitude of the blood pressure response during dipyridamole infusion were not different between the 2 groups. The rate-pressure product after dipyridamole infusion was significantly higher in patients with a normal ratio due to a greater increase in heart rate in this group.

Thallium-201 imaging correlates of increased lung/heart ratio:

Significantly more patients with an increased lung/heart thallium-201 ratio had myocardial segments showing initial defects, redistribution and fixed defects compared to those with a normal ratio (Figure 3). Left ventricular cavity dilatation on the initial anterior image was also more prevalent in the group with an increased compared to a normal lung/heart thallium-201 ratio. Patients with an increased lung/heart ratio had a greater number of segments exhibiting initial defects, redistribution and persistent defects than those without an increased ratio (Figure 4).

Multivariate analysis: Multiple stepwise linear regression analysis demonstrated that only 2 of the 24 variables analyzed were independently and significantly correlated with the lung/heart ratio of thallium-201. The presence of redistribution was found to be the strongest correlate of the lung/heart thallium-201 ratio ($r = 0.20$, $p < 0.0001$). Left ventricular dilatation, entered in the second step of the regression, was the only other significant correlate of an increased lung/heart

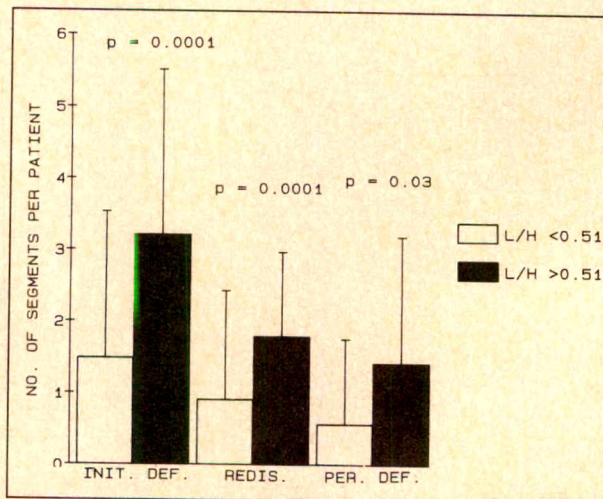


FIGURE 4. Comparison between patients with and without increased lung/heart (L/H) thallium-201 ratio in terms of the number of myocardial segments exhibiting initial (INIT.) redistribution (REDIS.) and persistent defects (PER. DEF.).

ratio ($r = 0.05$, $p = 0.02$). None of the other clinical and imaging variables that were significant on univariate analysis contributed additionally or independently to the correlation.

DISCUSSION

In the current study, 22% of the patients undergoing dipyridamole stress imaging were found to have increased lung/heart thallium-201 ratio, a rate similar to that of patients undergoing exercise stress imaging.^{1,3,6,8} The actual values of the lung/heart ratio for patients with normal and abnormal scans were comparable between the exercise and dipyridamole groups. On multivariate analysis, the presence of redistribution and transient cardiac dilatation were the only 2 variables that were found to correlate with the lung/heart thallium-201 ratio. The other 22 clinical and imaging variables analyzed in this study did not correlate with lung/heart thallium-201 ratio on multivariate analysis, although several were found to be associated with an increased ratio on univariate analysis.

Comparison of dipyridamole and exercise stress imaging: Because thallium-201 kinetics after dipyridamole infusion differ from that after exercise,²¹ one might not have readily predicted that the prevalence of increased lung thallium-201 activity during dipyridamole thallium-201 imaging would necessarily parallel that of exercise imaging. With exercise, there is splanchnic vasoconstriction with flow being diverted to the skeletal muscles and the heart. In contrast, organ blood flow distribution after administration of dipyridamole more closely resembles that at rest, resulting in greater background counts on initial dipyridamole images.²¹ The initial myocardial thallium-201 uptake after dipyridamole, however, tends to be relatively greater than that after exercise because of a more favorable coronary blood flow to cardiac output ratio.²¹ The net result is that the myocardial to background ratio is comparable in both exercise and dipyridamole imaging, which may partly explain similar prevalence and correlates of lung/heart thallium-201 ratio in the 2 tests.

Another reason one may not have predicted the lung/heart ratio during dipyridamole stress imaging to exhibit the same associations as during exercise imaging is that, in the former situation, thallium-201 is injected with the patient in the supine position where lung thallium-201 uptake is influenced by a greater pulmonary blood volume or increased pulmonary transit time. These reasons notwithstanding, our data suggest that the associations between increased lung/heart thallium-201 ratio during dipyridamole stress and exercise imaging are the same, suggesting a possible similar mechanism.

Clinical variables that correlate with lung/heart thallium-201 ratio: The variables found in this study to correlate with the lung/heart thallium-201 ratio are comparable to those previously described for increased ratio during exercise.^{1-3,4-6,8} Of the 17 clinical and stress nonimaging variables analyzed in our patients, 3 were found to be significant univariate correlates of an increased ratio: prior myocardial infarction, concomi-

tant β -blocker therapy, and lower rate pressure-product after dipyridamole infusion. A greater prevalence of prior myocardial infarction has been previously associated with increased lung/heart thallium-201 ratio.^{1,6} Unlike exercise, during dipyridamole infusion, enhanced chronotropic and inotropic responses would not be expected. Beta blockers, therefore, would not be expected to cause increased pulmonary thallium-201 uptake by inhibition of this mechanism. Rather, β -blocker use may be a marker of more severe coronary artery disease. A lower rate-pressure product after dipyridamole in patients with increased lung/heart ratio may imply ischemic left ventricular dysfunction in patients with more extensive coronary artery disease.⁶

Thallium-201 imaging variables that correlate with the lung/heart thallium-201 ratio: Thallium-201 imaging variables found in our study to be associated with increased lung uptake of thallium-201 are not unlike those described in studies using exercise stress imaging.^{1,3,6} With univariate analysis, we found that patients with an increased ratio were more likely to have a greater incidence and number of initial, transient and persistent thallium-201 perfusion defects, as well as left ventricular cavity dilatation. When multiple stepwise linear regression analysis was performed, the presence of redistribution was found to be the most powerful independent predictor of the lung/heart ratio. Left ventricular cavity dilatation was the only other variable that correlated with increased lung/heart ratio on multivariate analysis. The association of redistribution and left ventricular cavity dilatation with increased lung/heart thallium-201 ratio probably superseded the other associations found to be significant on univariate analysis.

Possible mechanisms of increased lung uptake during dipyridamole stress: Our data do not demonstrate the mechanism(s) by which increased pulmonary uptake of thallium-201 occurs during dipyridamole stress imaging. However, our data suggest that it is indicative of more severe coronary artery disease and transient left ventricular dysfunction consequent to administration of the vasodilator. In the canine model, pulmonary thallium-201 extraction has been shown to increase in the presence of increased left atrial pressure or pulmonary transit time.² Exercise-induced increases in pulmonary capillary wedge pressure has been also correlated with increased lung thallium-201 activity in patients.¹ Increased extravascular lung water, in a model of acute pulmonary edema, has been shown to have a linear relation to pulmonary thallium-201 uptake.²² We speculate that similar phenomena may explain increased lung thallium-201 uptake during dipyridamole imaging.

The increased lung thallium-201 uptake in our patients undergoing dipyridamole stress imaging occurred without a corresponding increase in the rate-pressure product, implying that if ischemia occurred, it was not primarily due to an increase in myocardial oxygen demand. Vasodilator-induced subendocardial hypoperfusion has been demonstrated in the canine model.^{23,24} The development of unfavorable endocardial/epicardial blood flow gradients distal to a critical stenosis after vasodilatation with dipyridamole may result from "cor-

onary steal.”²³⁻²⁸ In some patients receiving intravenous dipyridamole, regional lactate production was shown to occur in areas supplied by stenosed coronary arteries and was associated with distribution of flow away from these regions.²⁹ Dipyridamole-induced alterations in myocardial flow patterns could, therefore, be physiologically important and might produce ischemic left ventricular dysfunction sufficient to raise left ventricular filling pressure and thus, pulmonary capillary pressure.

Study limitations: This study defined an abnormal lung/heart ratio based on norms established in subjects with low likelihood of coronary artery disease undergoing exercise imaging. More acceptable criteria should probably be based on similar subjects receiving dipyridamole. However, given that the lung/heart ratios for normal and abnormal exercise images were virtually identical to those for dipyridamole images, we believe that the norms used in this study are acceptable. Another limitation of the study is that cardiac catheterization was not performed in most patients, and thus we could not assess coronary angiographic and hemodynamic correlates of increased lung/heart thallium-201 ratio. The only previously published study assessing the angiographic correlates of increased lung thallium-201 activity found lung/heart ratio of thallium-201 to be significantly correlated with the presence of coronary artery disease.³⁰ This study, using a smaller patient cohort, failed to demonstrate a relation between lung/heart thallium-201 ratio and both angiographically determined extent of coronary artery disease and resting left ventricular ejection fraction. However, left ventricular ejection fraction in this study was not measured after dipyridamole infusion.

Possible clinical implications: Our study suggests that pulmonary thallium-201 uptake may be a useful supplementary variable during dipyridamole thallium-201 imaging. Increased lung activity during exercise thallium-201 imaging bodes a poor prognosis.^{4,6,8-10} If increased lung thallium-201 uptake during dipyridamole imaging is indeed comparable both in its incidence and its pathogenesis to exercise stress imaging, it may also offer similar prognostic information. Further studies are required to address this issue.

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Sudden Death Behind the Wheel from Natural Disease in Drivers of Four-Wheeled Motorized Vehicles

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The heart was studied in 30 persons who died suddenly from natural causes in the driver's seat of an automobile, truck or bus. Twenty had cardiac arrest while driving and the other 10 while sitting in the driver's seat of a parked vehicle. Of the 20 drivers, 16 died from atherosclerotic coronary artery disease (CAD): 12 (75%) had minor collisions and 4 did not. Of the 16 with fatal CAD, an average of 2.3 ± 0.8 of the 4 major coronary arteries were narrowed $>75\%$ in cross-sectional area (CSA) by plaque; of 668 five-mm segments of the 4 major (right, left main, left anterior descending, left circumflex) coronary arteries in 13 of these 16 cases, 27 (4%) were narrowed 96 to 100% and 127 (19%) were narrowed 76 to 95% in CSA by plaque. The remaining 4 drivers died from noncoronary conditions: aortic rupture associated with the Marfan syndrome in 1; cardiac sarcoidosis in 1; thoracic aortic dissection in 1; and severe mitral regurgitation from infective endocarditis, which had healed in 1. The other 10 persons were found dead in the driver's seat of a parked vehicle and 8 of them had fatal CAD. Of the 8 CAD victims, an average of 2.5 ± 1.2 of the 4 major coronary arteries was narrowed $>75\%$ by plaque; of the 283 five-mm segments of coronary arteries in 7 of the 8 cases, 44 (16%) were narrowed 96 to 100% and 69 (24%) were narrowed 76 to 95% in CSA by plaque.

Victims dying suddenly from CAD while driving are similar to other out-of-hospital sudden coronary death victims with respect to mean age, gender, heart weight, frequency of healed myocardial infarcts, number of major epicardial coronary arteries severely narrowed, and the percentage of 5-mm-long segments of the major arteries severely narrowed by atherosclerotic plaque. Most drivers stopped the vehicle without injury to themselves or to others.

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In the USA approximately 50,000 deaths occur each year from accidents involving 4-wheeled motorized vehicles, a death rate of 20/100,000 population.¹ Most deaths are the result of trauma incurred by the accident. Some deaths, however, occur in occupants of 4-wheeled motorized vehicles as a result of natural causes, and an accident may or may not result when the sudden illness affects the vehicle's driver. The most common cause of sudden death from natural disease in drivers is cardiovascular disease, and coronary artery disease (CAD) is by far the most common of them. Myerburg and Davis² in 1964 analyzed medical examiners' reports in 1,348 cases of natural death from CAD in their local medical examiner's office, and found that 71 (5%) occurred in drivers; 24 accidents (34%), all minor, resulted from these 71 deaths. Bowen³ in 1973 analyzed medical examiner's reports in 9,330 cases of sudden death from CAD and found that 98 (1%) occurred in drivers: 46 accidents (47%), all minor, resulted from these 98 deaths. In the present report we examined the heart and major arteries and reports of other body organs in 30 persons who died behind the wheel from natural disease; 12 (40%) deaths resulted in accidents, all minor. The major focus of this report is on the extent of CAD present and on the frequency and types of myocardial lesions.

METHODS

Cases studied: Records from the Pathology Branch, National Heart, Lung, and Blood Institute, were searched for cases of sudden natural death that occurred in the driver's seat of automobiles, trucks, or buses. On the basis of findings at necropsy, the cases were divided into 3 groups: group I, fatal cardiac arrest from significant ($>75\%$ cross-sectional area [CSA] narrowing of 1 or more arteries) CAD while driving, 16 cases; group II, sudden natural death not due to CAD while driving, 4 cases; and group III, persons found dead in the driver's seat of a parked vehicle but who were not known to be driving at the onset of the terminal event, 10 cases. The autopsies in all 30 subjects were performed at 1 of 4 local institutions, and subsequently the hearts were submitted to the Pathology Branch for study. Available clinical records, autopsy records and police reports were examined in all 30 subjects.

Examination of heart: The hearts were fixed in 10% buffered formalin for at least 24 hours before weighing and examination. The major (left main, left anterior descending, left circumflex, and right) epicardial coronary arteries were excised intact after fixation. The arteries

TABLE I Clinical and Morphologic Observations of Drivers

Case	Cause of Death	Age (yrs) & Sex	History of AMI	CHF	Symptoms of Heart Disease (yrs)	Duration of	Blood Alcohol Present			SH	DM	HW (g)	LV		Chamber Dilation		No. of Major Coronary Arteries Narrowed >75% CSA	No. of 5-mm Segments Examined	Percent of 5-mm Segments Narrowed in CSA				Coronary Thrombus	
							N	F	RV				LV	0-25%	26-50%	51-75%			76-95%	96-100%				
16 Drivers with Cardiac Arrest Associated with Coronary Artery Disease While Driving and Without Significant Bodily Injury (Group I)																								
1	CAD	38M	0	0	0	—	—	0	—	—	480	0	0	+	0	3	47	6	9	40	32	13	0	
2	CAD	38M	—	+	3	—	—	0	—	—	550	0	+	(T)	+	2	37	22	24	35	19	0	0	
3	CAD	51M	—	—	—	—	—	0	—	—	555	0	+	(E)	+	1	63	41	30	25	3	0	0	
4	CAD	52M	+	—	—	2	—	—	—	—	370	0	0	0	0	2	41	10	22	49	20	0	0	
5	CAD	52M	+	+	—	10	—	—	+	—	370	+	(T)	+	(SE)	0	50	14	32	42	8	4	+	(NO)
6	CAD	53M	—	—	—	—	—	0	—	—	415	0	0	0	0	3	52	10	21	42	27	0	+	(O)
7	CAD	54M	+	+	—	1.3	—	0	+	—	690	0	+	(T)	0	3 (a)	0	—	—	—	—	—	—	—
8	CAD	54M	—	—	—	—	—	0	+	+	550	0	+	(T)	0	3	40	0	25	38	35	3	0	0
9	CAD	56M	—	—	—	—	—	0	—	—	490	0	+	(T)	+	3	60	8	15	43	20	13	0	0
10	CAD	56M	—	+	—	—	—	0	+	—	550	0	+	(E)	+	1	48 (b)	60	27	8	4	0	0	0
11	CAD	57M	—	+	—	—	—	—	+	—	430	0	+	(T)	0	2	43 (b)	49	21	16	14	0	0	0
12 (c)	CAD	60F	—	—	—	—	—	0	—	+	480	+	(T)	0	0	1	66	86	9	2	3	0	+	(NO)
13 (c, d)	CAD	60M	—	+	+	4	—	—	—	—	—	+	(T)	0	0	≥1	0	—	—	—	—	—	—	—
14	CAD	63M	—	—	—	—	—	0	—	—	590	0	+	(T)	0	2	0	—	—	—	—	—	—	—
15	CAD	63M	—	—	—	—	—	0	—	—	610	0	+	(SE)	+	2	59	19	17	39	22	3	0	0
16	CAD	66M	—	—	—	—	—	0	—	—	705	0	+	(T)	+	3	62	10	5	42	34	10	0	0
4 Drivers who Became Unconscious While Driving and Death was not from Coronary Artery Disease or Significant Bodily Injury (Group II)																								
17 (e)	Aortic rupture	21M	0	0	0	—	0	0	—	0	0	0	0	+	+	0	54	96	4	0	0	0	0	0
18 (f)	Cardiac sarcoidosis	35M	0	0	0	—	—	0	0	—	0	0	0	+	+	0	45	84	13	2	0	0	0	0
19 (g)	Healed IE, MR	37M	—	—	+	3	—	—	—	—	800	0	0	+	+	0	64	98	2	0	0	0	0	0
20 (h)	Aortic dissection	69F	—	—	—	—	—	—	—	—	400	0	0	0	0	2	31	16	13	48	19	3	0	0

(a) coronary bypass surgery and left ventricular aneurysm resection 9 months before death; one saphenous vein graft occluded at autopsy.

(b) left main coronary artery not available.

(c) severe aortic brain injury with fatal biologic death 2 weeks later.

(d) acute myocardial infarct 3 weeks before fatal cardiac arrest while driving.

(e) Marfan syndrome, aortic regurgitation, mitral valve prolapse.

(f) a passenger on the bus took over control and stopped the bus safely.

(g) backed into a fence, then stopped and died a few minutes later in the vehicle.

(h) functionally normal bicuspid aortic valve.

(i) right coronary artery from the left sinus of Valsalva; right coronary artery courses between the aorta and pulmonary trunk; healed right ventricular infarct; left main and left anterior descending coronary arteries not available.

(j) left anterior descending artery tunneled for 3 cm.

(k) sexual activity immediately before death.

(l) logging injured before death.

(m) left main, left anterior descending, and left circumflex coronary arteries not available.

AMI = acute myocardial infarct; AP = angina pectoris; CAD = coronary artery disease; CHF = congestive heart failure; CSA = cross-sectional area; DM = diabetes mellitus; E = subepicardial; F = fibrosis; HW = heart weight; IE = infective endocarditis; LV = left ventricle; MR = mitral regurgitation; N = necrosis; NO = nonocclusive; O = occlusive; RV = right ventricle; SAH = subarachnoid hemorrhage; SE = subendocardial; SH = history of systemic hypertension; T = transmural.

(a) coronary bypass surgery and left ventricular aneurysm resection 9 months before death; one saphenous vein graft occluded at autopsy.

(b) left main coronary artery not available.

(c) severe anoxic brain injury with biologic death 2 weeks later.

(d) acute myocardial infarct 3 weeks before fatal cardiac arrest while driving.

(e) Marfan syndrome, aortic regurgitation, mitral valve prolapse.

(f) a passenger on the bus took over control and stopped the bus safely.

(g) backed into a fence then stopped and died a few minutes later in the vehicle.

(h) functionally normal bicuspid aortic valve.

(i) right coronary artery from the left sinus of Valsalva; right coronary artery courses between the aorta and pulmonary trunk; healed right ventricular infarct; left main and left anterior descending coronary arteries not available.

(j) left anterior descending artery tunneled for 3 cm.

(k) sexual activity inferred immediately before death.

(l) jogging inferred before death.

(m) left main, left anterior descending, and left circumflex coronary arteries not available.

AMI = acute myocardial infarct; AP = angina pectoris; CAD = coronary artery disease; CHF = congestive heart failure; CSA = cross-sectional area; DM = diabetes mellitus; E = subepicardial; F = fibrosis; HW = heart weight; IE = infective endocarditis; LV = left ventricle; MR = mitral regurgitation; N = necrosis; NO = nonocclusive; O = occlusive; RV = right ventricle; SAH = subarachnoid hemorrhage; SE = subendocardial; SH = history of systemic hypertension; T = transmural.

TABLE I Continued

10 Victims Found Dead in the Driver's Seat of a Parked Vehicle and who were not Known to be Driving at the Onset of the Terminal Event (Group III)														
	SAH	38M	41M	49M	50M	51M	56M	56M	59M	59M	62F	0	0	0
21	SAH	—	—	—	—	—	—	—	—	—	—	—	—	—
22	CAD	—	—	—	—	—	—	—	—	—	—	—	—	—
23 (i)	CAD	—	—	—	—	—	—	—	—	—	—	—	—	—
24	CAD	—	—	—	—	—	—	—	—	—	—	—	—	—
25	Unknown	—	—	—	—	—	—	—	—	—	—	—	—	—
26 (i)	CAD	—	—	—	—	—	—	—	—	—	—	—	—	—
27	CAD	—	—	—	—	—	—	—	—	—	—	—	—	—
28 (k)	CAD	—	—	—	—	—	—	—	—	—	—	—	—	—
29 (i)	CAD	—	—	—	—	—	—	—	—	—	—	—	—	—
30	CAD	—	—	—	—	—	—	—	—	—	—	—	—	—

(a) coronary bypass surgery and left ventricular aneurysm resection 9 months before death; one saphenous vein graft occluded at autopsy.

(b) left main coronary artery not available.

(c) severe aortic dissection with biologic death 2 weeks later.

(d) acute myocardial infarct 3 weeks before fatal cardiac arrest while driving.

(e) acute myocardial infarct, aortic regurgitation, mitral valve prolapse.

(f) Marfan syndrome, the bus took over control and stopped the bus safely.

(g) a passenger on the bus then stopped and died a few minutes later in the vehicle.

(h) functionally normal bicuspid aortic valve.

(i) left coronary artery from the left sinus of Valsalva; right coronary artery courses between the aorta and pulmonary trunk; healed right ventricular infarct; left main and left anterior descending coronary arteries not available.

(j) left anterior descending artery tunneled for 3 cm.

(k) sudden activity inferred immediately before death.

(l) plaque inferred before death.

(m) plaque in left anterior descending, and left circumflex coronary arteries not available.

AMI = acute myocardial infarct; AP = angina pectoris; CAD = coronary artery disease; CHF = congestive heart failure; CSA = cross-sectional area; DM = diabetes mellitus; E = subepicardial; F = fibrosis; HW = heart weight; IE = infective endocarditis; LV = left ventricle; MR = mitral regurgitation; N = necrosis; NO = nonocclusive; O = occlusive; SAH = subarachnoid hemorrhage; SE = subendocardial; SH = history of systemic hypertension; T = transmural.

TABLE II Clinical and Cardiac Morphologic Observations in the 30 Drivers

	Group I Sudden Death While Driving Due to CAD (n = 16)	Group II Sudden Death While Driving Not Due to CAD (n = 4)	Group III Sudden Death Behind Wheel Vehicle Parked (n = 10)
Mean age \pm SD (years)	55 \pm 8	41 \pm 20	52 \pm 8
Men/women	15/1	3/1	9/1
Angina pectoris	3	0	2
Past acute myocardial infarction (history)	6	0	2
Congestive heart failure (history)	4	1	2
Systemic hyper- tension (history)	5	0	3
Diabetes mellitus (history)	2	0	0
Type of collision (no.):			
None	4	3	10
Parked vehicles only	4	0	—
Single-MVA, no parked vehicles	5	1	—
Multiple-MVA	3	0	—
Damage to driver's vehicle (no.):			
None	5	4	10
Minor	10	0	—
Major	1	0	—
Damage to other vehicles (no.):			
Minor	9	0	—
Major	1	0	—
Property damage (no.)	4	1	—
Blood alcohol present	0	0	1
Heart weight \pm SD (g)	522 \pm 103 (15)	558 \pm 176	463 \pm 135
HW >400 g (men); HW >350 g (women)	13/15	4	7
LV necrosis	3	0	0
LV fibrosis	12	0	4
RV dilation	7	3	2
LV dilation	9	3	5
No. of CAs narrowed >75% in CSA by plaque:			
0	0	3	2
1	3*	0	2
2	5*	1	2
3	7*	0	2
4	0*	0	2
Mean No. of CAs narrowed >75% in CSA by plaque \pm SD	2.3 \pm 0.8*	0.5 \pm 1.0	2.0 \pm 1.5
Nonocclusive coronary thrombus	2/13	0	0/7
Occlusive coronary thrombus	1/13	0	1/7

* One victim was not included here because although at least 1 coronary artery was severely narrowed, it was not known precisely how many were severely narrowed.

CA = coronary artery; MVA = motor vehicle accident; SD = standard deviation; other abbreviations as in Table I.

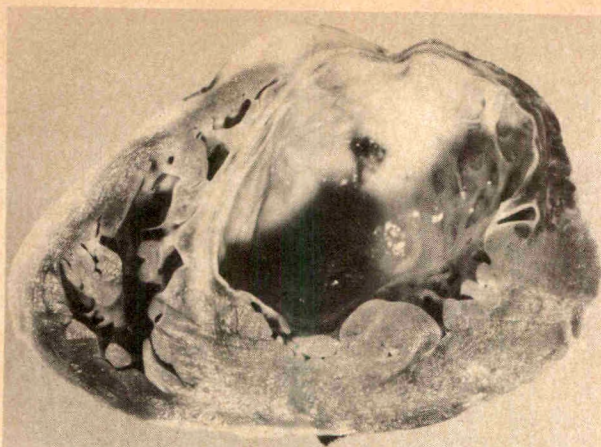


FIGURE 1. Case 2, Table I. Opened cardiac ventricles showing a healed large anterior wall infarct which is aneurysmal in a 38-year-old man (DCMEO #85-07-598). He had had evidence of congestive heart failure before his sudden death while driving.

then were decalcified if necessary with formic acid-sodium citrate for at least 24 hours. The coronary arteries then were cut transversely into 5-mm-long segments and labeled sequentially from origin to termination by a method described elsewhere.⁴ The 5-mm segments were dehydrated in ethanol and xylene, and embedded in paraffin. At least one 6- μ -thick histologic section was cut from each 5-mm segment and stained by the Movat method. The percent CSA luminal narrowing by atherosclerotic plaque was determined by microscopic examination with approximately 40 times magnification. The percent luminal narrowing was graded into 1 of 5 CSA categories: 0 to 25, 26 to 50, 51 to 75, 76 to 95 and 95 to 100%. The accuracy of this technique of grading CSA narrowing has been validated to be >95%.⁵ Histologic sections, at least 2 per heart, extending from

endocardium to epicardium of the left ventricle, were prepared. Foci of myocardial necrosis or fibrosis were confirmed histologically.

RESULTS

Clinical and terminal event features in each of the 30 subjects, divided by the 3 groups, are detailed in Table I, summarized in Table II, and some hearts are illustrated in Figures 1 to 7.

Etiology of deaths: All 20 subjects who died suddenly from natural causes while driving (groups I and II) died from cardiovascular disease: CAD in 16 (80%) and 1 each from rupture of the thoracic aorta in the Marfan syndrome; cardiac sarcoidosis; severe mitral regurgitation from infective endocarditis that had healed; and rupture of an aortic dissection. Of the 10 persons found dead in the driver's seat of a parked vehicle (group III), 8 died from CAD. Case 23 (Table I) had origin of the right coronary artery from the left sinus of Valsalva and it coursed between the aorta and pulmonary trunk.

Previous symptomatic myocardial ischemia: Angina pectoris or acute myocardial infarction that had healed and/or congestive heart failure was known to be present in 7 (44%) of the 16 group I subjects, in none of the 4 group II subjects, and in 6 of the 10 group III victims. A coronary bypass operation with simultaneous resection of a left ventricular aneurysm had been performed earlier in 1 subject (case 7).

Accidents: Among the 16 group I cases, 4 collisions occurred with parked vehicles only, 5 collisions involved property damage apart from other vehicles, 3 collisions were with other operating vehicles (1 head-on, 1 broadside, 1 rear-end), and no collision occurred in 4 cases. Therefore, an accident occurred in 12 (75%) group I subjects. These collisions resulted in minor damage to 10 drivers' vehicles and to 9 other vehicles, and major damage to 1 driver's vehicle and to 1 other vehicle. Only

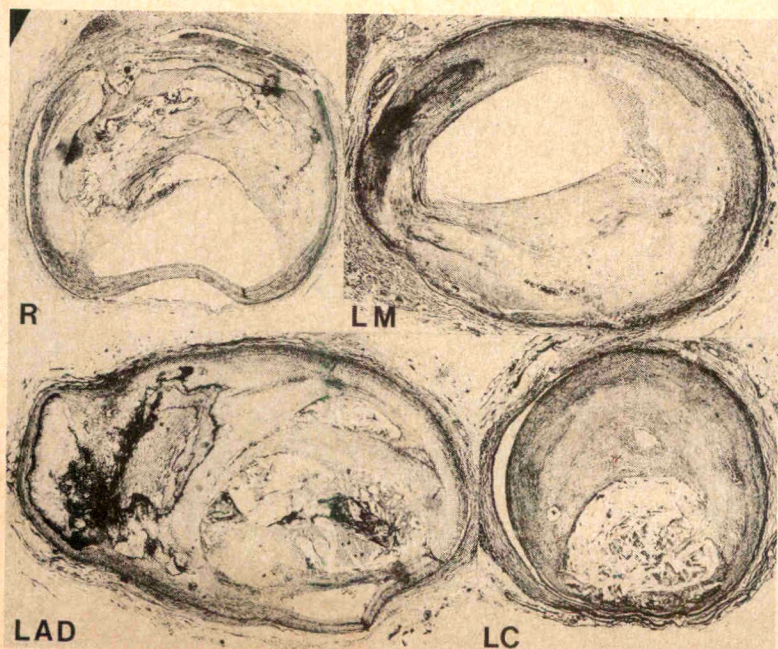


FIGURE 2. Case 5. Photomicrographs of sites of maximal narrowing of the right (R), left main (LM), left anterior descending (LAD) and left circumflex (LC) coronary arteries in a 52-year-old man (SH #A80-47) with previous angina pectoris. A large acute myocardial infarct was found at necropsy. (Movat stain, original magnification of each $\times 26$, reduced 34%.)

1 collision occurred in the 4 group II subjects, and it involved non-vehicle property damage and no damage to the driver's vehicle. In case 18, an accident was prevented by a passenger on the bus who took over control when the driver collapsed. In the 16 group I subjects, 4 (25%) received minor body injuries. Only 1 driver in group I had passengers, and the 3 passengers in his taxi were not injured in the collision. No injuries and no fatalities occurred to passengers in the drivers' vehicles, to occupants of other vehicles or to pedestrians.

Blood alcohol levels: No blood alcohol or illicit mind-altering drugs were present in any of the drivers in whom this information was known (Table I). The cause of death was undetermined in the 1 subject with a positive blood alcohol level (case 25).

Myocardial damage: Left ventricular necrosis was present in 3 (19%) of the 16 drivers in group I; 2 of these drivers (cases 12 and 13) had been severely brain injured from anoxia during the cardiac arrest while driving and proceeded to biologic death 2 weeks later. In addition, case 13 had been hospitalized for an acute myocardial infarct 3 weeks before the cardiac arrest while driving. Left ventricular fibrosis was present in 12 (75%) of the 16 group I victims, and in 4 of the 10 group III victims.

Coronary arteries: In the 16 drivers who died suddenly from CAD, the mean number of coronary arteries narrowed >75% in CSA by atherosclerotic plaque was 2.3 (standard deviation 0.8): 3 (20%) had 1 artery so narrowed; 5 (33%) had 2 arteries, and 7 (47%) had 3 arteries so narrowed. One had >75% CSA narrowing of at least 1 coronary artery, but the exact number so narrowed is not known. None had a left main coronary artery narrowed >75% in CSA. In addition, the 1 subject with previous cardiac surgery (case 7) had total oc-

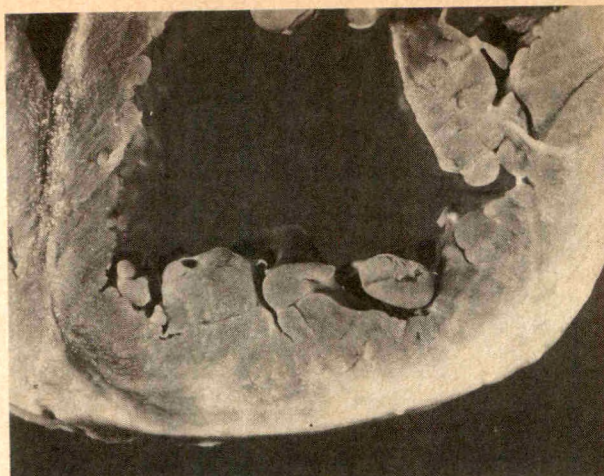


FIGURE 3. Case 10. Healed subepicardial infarct of the left ventricular free wall with left ventricular dilation in a 56-year-old man (DCMEO #88-01-68) with a previous clinical event compatible with acute myocardial infarction with evidence of congestive heart failure thereafter.

clusion of 1 of 2 saphenous vein bypass grafts. The coronary arteries were available for histologic review in 13 of 16 group I cases, and from them 668 five-mm-long segments were examined. The mean percents of 5-mm segments narrowed in CSA by 0 to 25, 26 to 50, 51 to 75, 76 to 95 and 96 to 100% were 26, 20, 33, 19 and 4%, respectively. In the 8 group III victims with CAD, the mean number of major epicardial coronary arteries narrowed >75% CSA was 2.5 (standard deviation 1.2): 2 had 1 artery so narrowed; 2 had 2 arteries so narrowed; 2 had 3 arteries so narrowed; and 2 had 4 arteries so narrowed. Of the 283 five-mm segments of coronary artery in 7 of these 8 victims, 44 (16%) were nar-

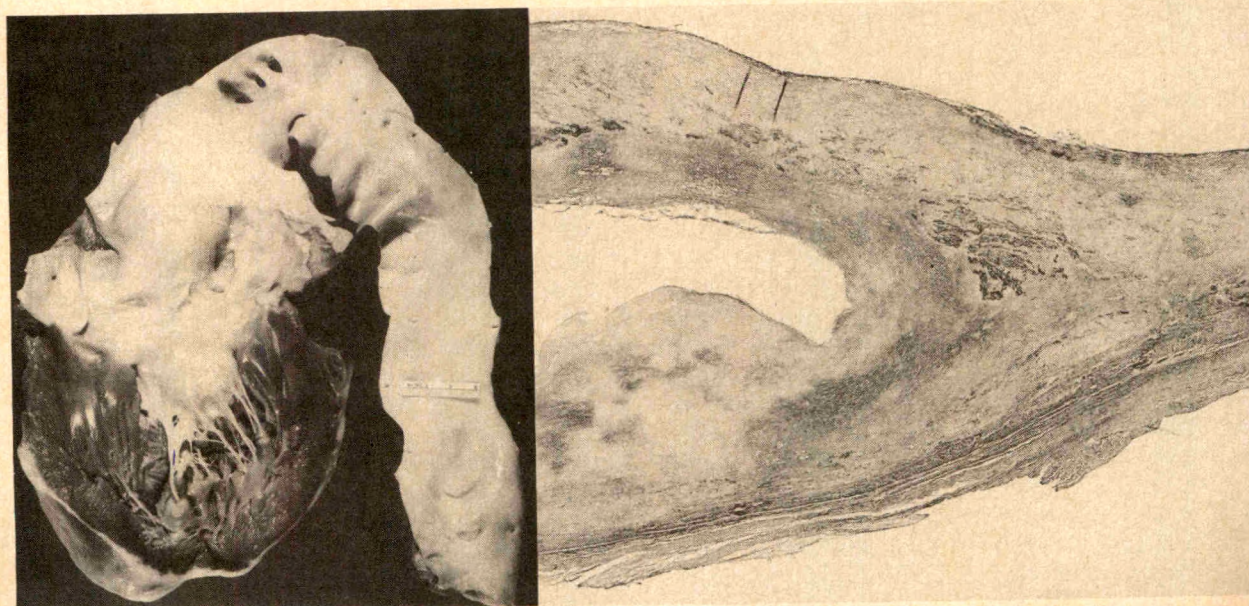


FIGURE 4. Case 17. Heart and aorta in a 21-year-old man (A67-120) with the Marfan syndrome who died suddenly from rupture of the thoracic aorta after parking his car in his garage. A tear is present in the ascending aorta, which is quite dilated. This patient was known to have had aortic regurgitation since childhood. A photomicrograph of a healed tear in ascending aorta is shown on the right. The media is virtually depleted of elastic fibers, the classic aortic lesion of the Marfan syndrome. (Elastic van Gieson stain, original magnification $\times 19$, reduced 23%.)

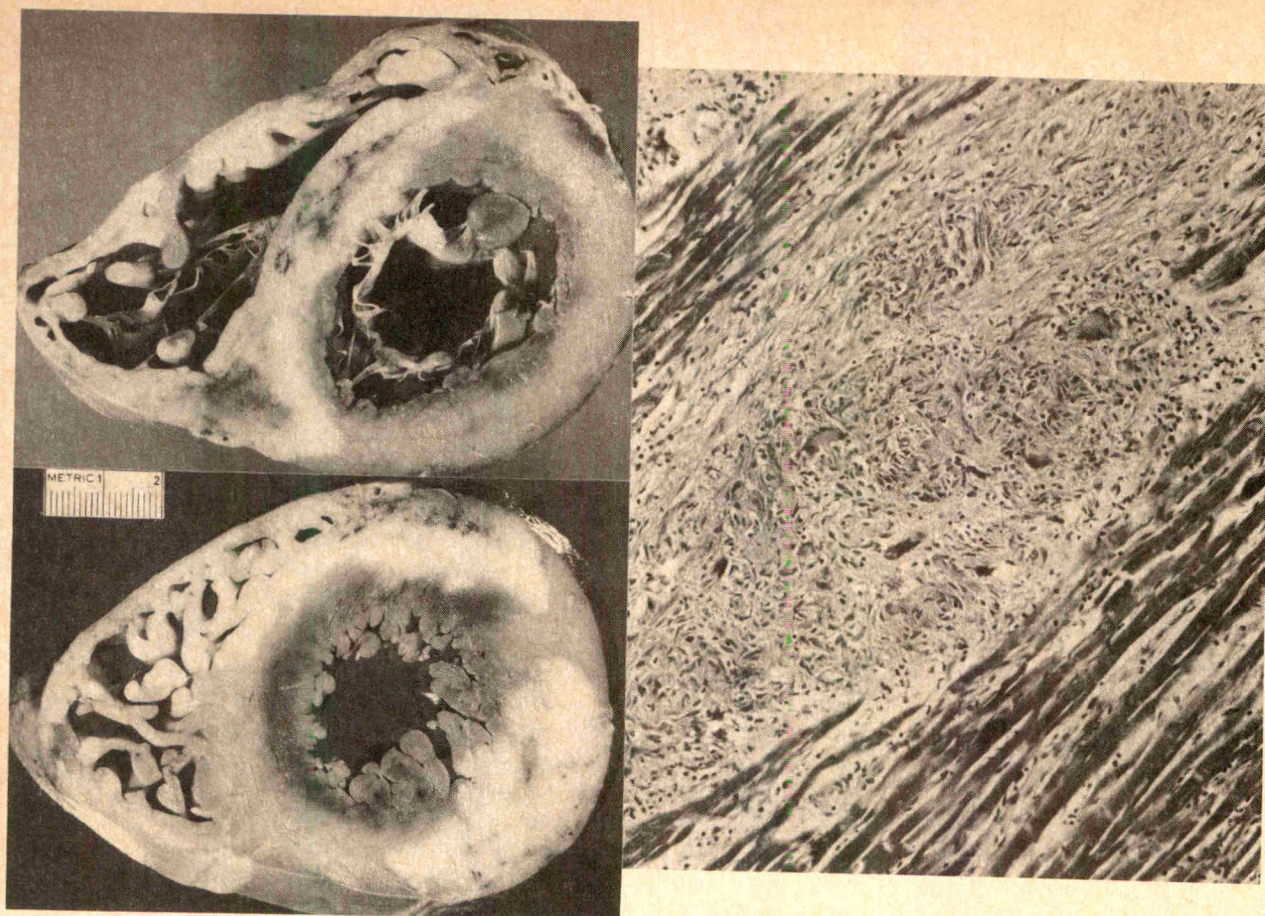


FIGURE 5. Case 18. Two views (left) of the cardiac ventricles showing extensive replacement of myocardium of the right ventricular wall, ventricular septum, and left ventricular wall in a 35-year-old man (DCME #88-01-140) who died suddenly from cardiac sarcoidosis while operating a bus. Photomicrograph (right) of portion of left ventricular wall. (Hematoxylin and eosin stain, original magnification $\times 300$, reduced 25%.)

rowed 96 to 100% and 69 (24%) were narrowed 76 to 95% in CSA by plaque.

DISCUSSION

Death in 29 of the aforementioned 30 drivers was the result of a cardiovascular condition, CAD in 24 (80%). The mean age of the 24 CAD victims was 54 ± 7 years and most (92%) were men. This age is similar to that of out-of-hospital nondriving sudden coronary death victims.^{3,6-9} The preponderance of men may be explained by 2 factors: (1) Men die suddenly from CAD more often than do women, and (2) men drive more than women.¹⁰ Previous clinical evidence of heart disease is fairly common in persons dying from heart disease behind the wheel, occurring in 13 (43%) of our 30 victims, and in 17 to 67% of such previously reported victims.^{2,3,8-10}

Among the 20 drivers dying suddenly from natural disease, a collision occurred in 12 cases, 4 drivers received injuries (all minor), and no other persons received injuries. This proportion of cases involving collisions is similar to previously published studies that have ranged from 26 to 67%.^{2,3,8,9,11-13} Setting features such as the density of vehicles on the roads, road speed limits,

and the number of other persons at risk for injury are important when considering observations of collisions, property damage, and injury to others. Among the 16 drivers dying from CAD while driving, the vehicle was brought to a safe stop without collision in 4 (25%) cases. Kerwin¹⁴ suggested that electrical disturbances in the heart "may take sufficient time to evolve that some cerebral circulation is maintained for a brief time. The driver therefore has a warning period during which a serious accident can be and nearly always is avoided."

Few previous studies of natural sudden death while driving or at the wheel have noted heart weights or the frequency of myocardial necrosis and healed infarcts. Cardiomegaly was present in 13 (87%) of 15 hearts in the drivers dying suddenly from CAD and in 6 (75%) of the 8 persons dying from CAD in the parked vehicle group; respective mean heart weights were 522 and 479 g. These heart weights and proportions of cardiomegaly are similar to those of out-of-hospital nondriving sudden coronary death victims.⁷ Three victims who died from CAD had transmural necrosis. Previous reports of sudden coronary death while driving or behind the wheel have found the proportion with myocardial necrosis to be 2%,³ 22%⁹ and 39%.⁸ Most drivers dying suddenly



FIGURE 6. Case 29. A portion of the cardiac ventricles showing a healed infarct of the anterolateral left ventricular wall in a 59-year-old man (NNMC #A79-148) with a previous clinical event 4 years earlier compatible with acute myocardial infarction. He was found dead in his car. He had returned to his car shortly after jogging.

from CAD have healed myocardial infarcts: 67% in our 24 cases, and 56%^{3,8} and 67%⁹ in previously published reports.

One previous autopsy study of natural sudden deaths "in motor vehicles" (both drivers and nondrivers, both moving and parked vehicles) reported the extent of the coronary atherosclerosis. The study by Copeland¹² involved 133 autopsied cases of natural sudden death that occurred "in a motor vehicle," and in 106 of the 133 cases the coronary arteries were examined: in 70 (66%) victims 1 or more coronary arteries were narrowed 76 to 100% in CSA. In our study, the mean number of major epicardial coronary arteries narrowed >75% CSA was 2.3. In comparison, of 230 out-of-hospital and out-of-automobile sudden coronary death victims,⁷ the mean number of major epicardial coronary arteries narrowed >75% CSA by plaque was 2.4.

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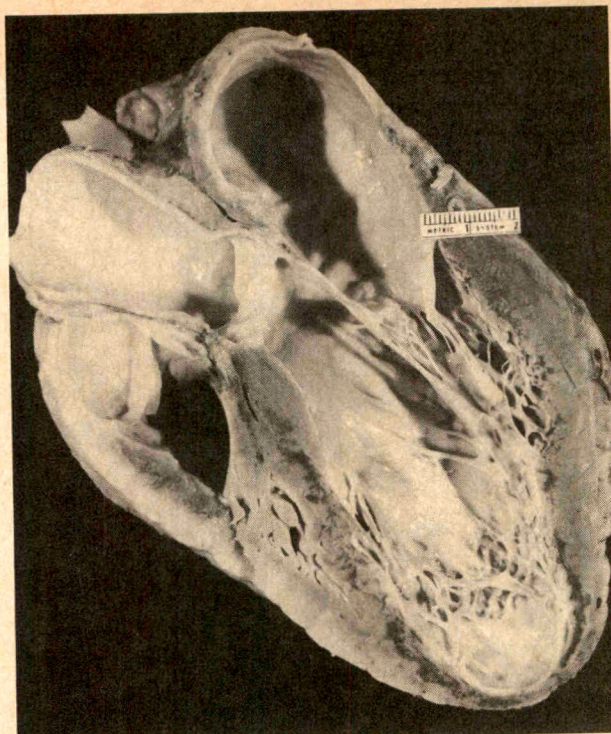


FIGURE 7. Case 30. Longitudinal view of the heart showing a dilated left ventricle with a large healed infarct in a 62-year-old woman (DCMO #79-02-133) who had had congestive heart failure. She was found dead after a snowstorm in her car, which was parked on the street.

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Changes in Plasma Free Fatty Acids and Glycerols During Prolonged Exercise in Trained and Hypertensive Persons Taking Propranolol and Pindolol

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The extent to which lipolysis is attenuated during prolonged submaximal exercise during β blockade was determined in 12 normotensive endurance-trained and 12 hypertensive sedentary men using nonselective drugs with and without intrinsic sympathomimetic activity (ISA). Initially, subjects performed a graded treadmill test to determine maximal oxygen uptake ($\dot{V}O_{2\max}$). This was followed by 2-hour walks at 25 and 45% of the subject's $\dot{V}O_{2\max}$ under each of 3 treatments: pindolol (ISA), propranolol (non-ISA) and placebo. The distribution of medication was randomized and double blinded. Blood samples taken at rest and every 30 minutes during the 2-hour walks were analyzed to determine the concentrations of free fatty acids (FFA) and glycerol. On the basis of the respective changes in FFA, glycerols and the respiratory exchange ratio, β -adrenergic blockade did not attenuate lipolysis in the untrained hypertensive subjects when compared with the placebo administration. However, β blockade did demonstrate a tendency to attenuate lipolysis in the trained, normotensive subjects when compared with results after placebo administration. This was particularly evident at 30 minutes of exercise, when both glycerol and FFA concentrations were not increased above resting values under both conditions of β blockade. No differences between pindolol and propranolol were observed. Therefore, a β -blocking agent with ISA properties appears to have no clear benefit with respect to lipid metabolism during low and moderate intensity exercise. Furthermore, these data demonstrate that β blockade does not inhibit exercise-induced lipolysis at low and moderate intensities of

exercise as formerly believed, and is unlikely to be the cause of fatigue normally observed during work in patient populations taking β -blocking medication. (Am J Cardiol 1990;66:1336-1341)

The effects of β -adrenergic blockade on physical activity have recently been reviewed.¹⁻³ Lipolysis is one of the many adrenergically controlled processes affected by β blockade. During a prolonged bout of low-intensity exercise, triglycerides are broken down into glycerols and free fatty acids (FFA) in the adipocyte and muscle to provide metabolic substrate for the active muscle. With β blockade, however, the rate of lipolysis is attenuated,¹ increasing the potential for a reduced exercise capacity. In previous research studies, β blockers have been shown to attenuate the release of FFA and glycerols during exercise,⁴⁻¹⁷ although in 1 study FFA levels were higher when subjects were given β blockade than when given placebo at the end of a 1-hour run.¹⁸ Juhlin-Dannfelt¹⁹ concluded that the reduction in working capacity produced by β blockade during prolonged exercise is due to the metabolic effects caused by a decreased rate of lipolysis, reducing the availability of FFA, leading to the rapid depletion of liver and muscle glycogen stores, and therefore limiting cardiorespiratory endurance.

The purpose of the present study was to investigate the effects of β -adrenergic blockers, both with and without intrinsic sympathomimetic activity (ISA), on FFA and glycerol blood levels during prolonged submaximal exercise of low and moderate intensity, in endurance-trained normotensive and untrained hypertensive subjects. Rates of work were selected that approximate the range of rates most likely experienced by patients taking β -blocking medication. It was hypothesized that both groups would experience an attenuation in the increase of FFA and glycerol levels during exercise while taking β -adrenergic blockade; that this attenuation would not be as marked with ISA as with non-ISA treatment; that the attenuation would be greater in the endurance-trained group who have an increased reliance on fat as a metabolic substrate as a result of training²⁰; and that the effects of the ISA would be lost at the higher intensity of exercise.

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METHODS

The 24 men aged 18 to 34 years were recruited from the student, faculty and staff population at a major university. Of these, 12 subjects were untrained, relatively sedentary, hypertensive persons, having a diastolic blood pressure ≥ 95 mm Hg on 3 separate days. The other 12 subjects were normotensive and endurance-trained runners who were able to run 10 miles in <1 hour, or who ran a minimum of 35 to 40 miles/week. Ideally, this study would have been conducted exclusively on hypertensive subjects. However, it was not possible to recruit a sufficient number of highly trained hypertensive subjects. The subject characteristics are presented in Table I. Subjects taking some form of antihypertensive medication discontinued their medication 2 weeks before the initial testing, with the consent of their physician. Each subject provided an informed consent. This study was approved by the university's Institutional Review Board.

A brief medical history was obtained and a physical examination was performed on all subjects. An initial graded exercise test was conducted to determine the subject's maximal oxygen uptake ($\dot{V}O_{2\max}$) under non-medicated conditions. The protocol for this test has been reported previously.²¹ After the initial graded exercise test, the subject began 1 of 3 treatments: propranolol (160 mg/day), pindolol (10 mg/day) or placebo. The distribution of medication was randomized and double blinded.

The subject started the first treatment on the morning of day 1, taking 1 pill every 12 hours for days 1 to 9. The subject was asked to document the day and time each pill was taken. Compliance was monitored by pill counts. Treadmill tests were conducted on days 3, 7 and 9. The subject received medication 1.5 hours before exercise and was told not to eat 12 hours before test time. On day 3, a submaximal/maximal graded exercise test was performed.²¹ On day 7, a 2-hour walk at 25% of $\dot{V}O_{2\max}$ was performed. An 18G \times 2" intravenous catheter was inserted into the antecubital vein for blood sampling at rest and every 30 minutes during the 2-hour walk. Supine blood pressure and electrocardiograms were recorded before exercise. During quiet sitting and every 30 minutes while walking, $\dot{V}O_2$, stroke volume and cardiac output were measured at steady state using a Horizon Metabolic Measurement Cart. Blood pressure, rating of perceived exertion and an electrocardiogram were recorded every 15 minutes throughout the 2-hour bout of exercise. On day 9, the subject repeated the same protocol used on day 7, but at 45% of his $\dot{V}O_{2\max}$.

After the 2-hour walk at 45% of $\dot{V}O_{2\max}$, the subject stopped the first medication and began a 5-day washout period (days 10 to 14). On day 15, the subject started the second medication, following the same procedure as with the first medication, i.e., a submaximal/maximal graded exercise test, 2-hour walks at 25 and 45% of $\dot{V}O_{2\max}$, and a 5-day washout period. After the second washout period, the subject started the third medication, again repeating the same format as used for the first 2 medications.

At rest and every 30 minutes during the 2-hour walks at 25 and 45% of the subject's $\dot{V}O_{2\max}$, 5 ml of

TABLE I Characteristics of the Subject Population

Variable	Untrained Hypertensives		Trained Normotensives	
	Mean	SD	Mean	SD
Age (yrs)	25	4.8	24	3.3
Height (cm)	176	4.8	178	5.6
Weight (kg)	87	9.5	70	5.2
$\dot{V}O_{2\max}$ (ml \cdot kg ⁻¹ \cdot min ⁻¹)	40	7.4	60	5.4

SD = standard deviation.

blood was drawn from the catheter and mixed with 0.5 ml of ethylenediaminetetraacetic acid (24 mg/ml, pH 7.4). One ml of blood was then added to 2 ml of 8% perchloric acid, centrifuged, and the acid extract stored at 4°C for further analysis of glycerol. Blood glycerol concentration was determined enzymatically as described by Wieland.²² The initial blood samples were also centrifuged and the recovered plasma used for FFA analysis. Plasma FFA concentration was determined using Duncombe's modified FFA protocol.²³

This report focuses on the changes in FFA and glycerol during the 2-hour walks, under the 3 treatments, at 25 and 45% of $\dot{V}O_{2\max}$. A previous report presented the cardiovascular data during the submaximal and maximal exercise tests for the hypertensive subjects.²¹ To assess the effects of each drug, the Biomedical Statistical Package for 3-way analysis of variance (time, treatment, work rate) using repeated measures (BMDP2V) was used. The Neuman-Keuls post hoc analysis was used when differences between drugs or differences over time within a single exercise intensity were observed. Significance was established at $p < 0.05$.

RESULTS

Untrained subjects: Increases in both plasma FFA and glycerol concentrations were observed during 2 hours of treadmill walking in untrained hypertensive subjects; however, no significant differences between exercise intensities (25 vs 45% $\dot{V}O_{2\max}$) or between treatments (propranolol, pindolol, placebo) were seen. Since no differences were observed, FFA concentrations obtained from the 2 exercise intensities were averaged for a given time period for statistical purposes to establish a general trend in FFA concentrations over time (Figure 1). Plasma glycerol concentrations were averaged in a similar manner (Figure 1). Plasma FFA concentrations increased significantly over time from rest through 120 minutes of exercise. Increases in FFA concentrations between 30 and 120 minutes of exercise were also significant, indicating a sustained increase throughout exercise, not just during the transition from rest to exercise. Plasma glycerol levels increased significantly over time from rest through 120 minutes of exercise, and between 30 and 120 minutes.

Respiratory exchange ratio values increased quickly within the first 30 minutes of exercise and then gradually decreased between 30 and 120 minutes of exercise. No differences between treatments or between work rates were observed (Figure 1). When looking at the

general trend in respiratory exchange ratio over time, the values at rest were significantly lower than at 30, 60 and 90 minutes of exercise. Significant decreases in respiratory exchange ratio values were seen between 30 and 120 minutes of exercise.

Trained subjects: In the trained normotensive subjects, an increase in FFA concentration over time was observed during the 2-hour walks, but no differences were observed between exercise intensities (25 vs 45% of $\dot{V}O_2\text{max}$) or between treatments (propranolol, pindolol,

placebo). When all FFA values for both exercise intensities were averaged for a given time period, the general trend showed FFA levels increasing over time (Figure 2). FFA concentration increased significantly between 30 and 120 minutes of exercise for all 3 treatments, although there was no significant increase during the first 30 minutes compared to resting values when β blocked.

No differences in glycerol concentrations between exercise intensities were seen. When averaged across

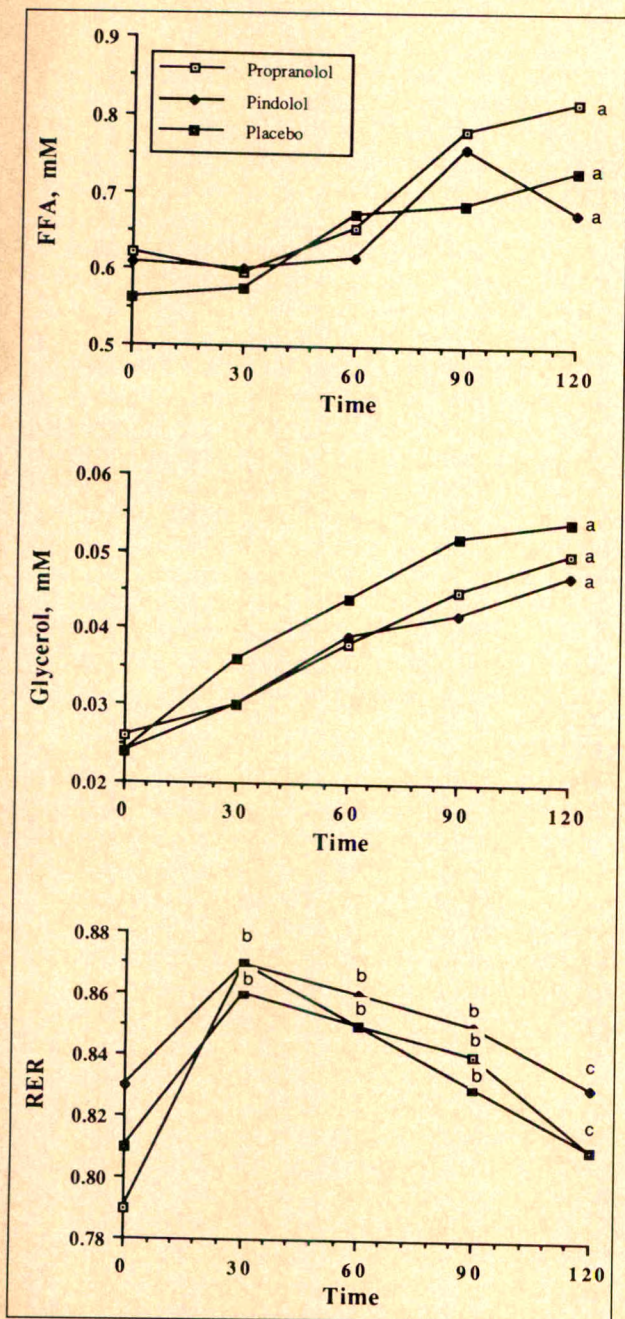


FIGURE 1. Changes in free fatty acids (FFA), glycerol and respiratory exchange ratio (RER) during 2-hour walks in the untrained subjects. a = significantly different ($p < 0.05$) from times 0 and 30 minutes; b = significantly different ($p < 0.05$) from time 0; and c = significantly different ($p < 0.05$) from time 30 minutes.

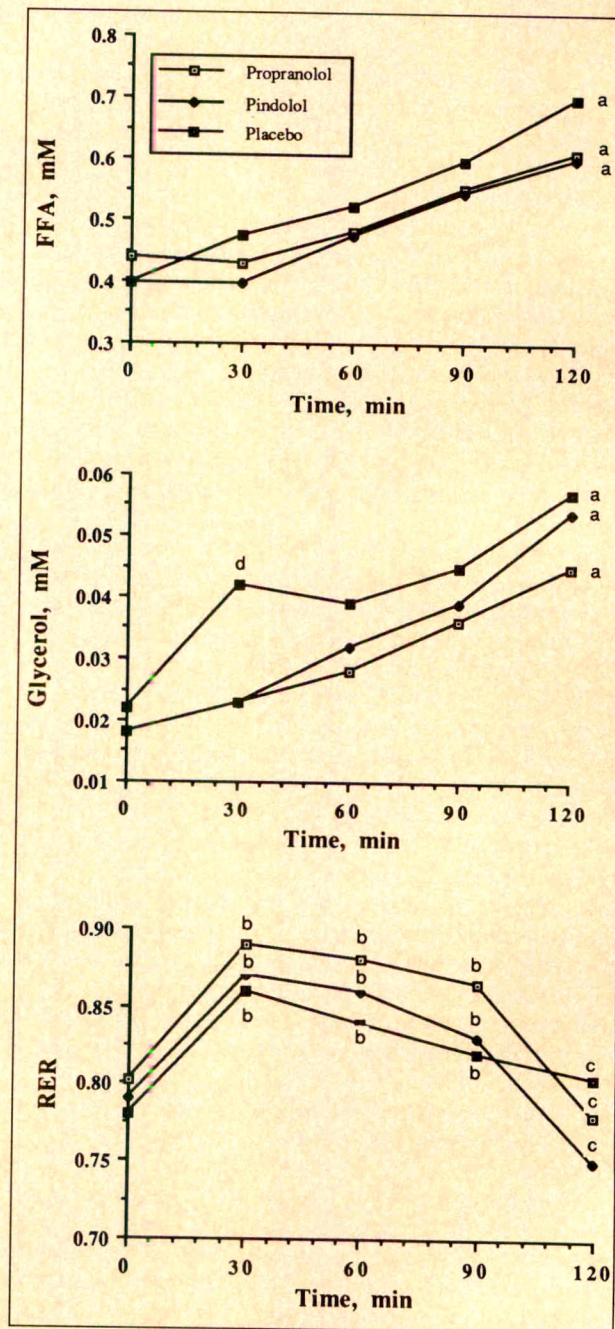


FIGURE 2. Changes in free fatty acids (FFA), glycerol and respiratory exchange ratio (RER) during 2-hour walks in the trained subjects. a = significantly different ($p < 0.05$) from times 0 and 30 minutes; b = significantly different ($p < 0.05$) from time 0; c = significantly different ($p < 0.05$) from time 30 minutes; and d = placebo significantly different compared to pindolol and propranolol.

the 2 exercise intensities, the general trend in plasma glycerols showed a significant increase between rest and 120 minutes, and between 30 and 120 minutes of exercise (Figure 2). When glycerol concentrations between treatments were compared, significant differences were observed at 30 minutes of exercise. Glycerol concentrations during placebo administration were significantly higher than during propranolol and pindolol administration. Differences between propranolol and placebo and between pindolol and placebo conditions at 60, 90 and 120 minutes of exercise approached, but did not reach, statistical significance. It appears that β blockade attenuated the onset of exercise-induced lipolysis in these trained subjects, but then had little effect on the subsequent rate of rise of glycerol throughout the remaining 90 minutes of exercise.

Respiratory exchange ratio values increased quickly within the first 30 minutes of exercise, and then gradually declined between 30 and 120 minutes of exercise. No significant differences between treatments or between exercise intensities were observed. When all respiratory exchange ratio values for a given period of time were averaged across the 2 exercise intensities, a gradual decline was observed after 30 minutes of exercise (Figure 2), i.e., the values decreased significantly between 30 and 120 minutes of exercise. At rest, the respiratory exchange ratio values were significantly lower than at 30, 60 and 90 minutes of exercise.

DISCUSSION

Because there are 2 independent variables differentiating the groups used in this study (i.e., trained versus untrained and normotensive versus hypertensive), no direct comparisons between groups are made. Therefore, the results for these 2 groups are discussed separately.

Untrained subjects: During the 2-hour walks, plasma FFA and glycerol levels increased over time in the untrained hypertensive subjects. Thus, as the subject initiated activity, an increased sympathetic drive stimulated fat catabolism, thereby increasing the energy supply to the working muscles. Within the first 60 minutes of exercise, this resulted in an increased amount of FFA and glycerol in the blood. The relative increase in glycerol levels was greater than the relative increase in FFA levels between rest and 30 minutes of exercise. Carlson et al²⁴ showed that plasma FFA uptake and utilization are affected by the esterification and hydrolysis of muscle triglyceride during endurance exercise. According to Franz et al,⁴ in addition to the FFA oxidized, some plasma FFA may be used to continuously replace the hydrolyzed muscular triglycerides, thereby further reducing FFA in the blood. Also, according to Franz et al,⁴ glycerol levels are a better indicator of lipolytic rate than are FFA levels. As seen in Figure 1, glycerol levels continued to rise steadily in these untrained hypertensive subjects. FFA levels also increased, but this increase occurred primarily after 30 minutes of exercise. Hence, lipolysis did increase over time as indicated by the rising concentrations of plasma FFA and glycerol coupled with the decline observed in the respiratory exchange ratio. With an increased reliance on fat as a

primary substrate for energy, there is a decrease in the ratio of carbon dioxide produced/oxygen consumed, thereby reducing the respiratory exchange ratio value. Despite the fact that these subjects were working at a constant rate, an increased lipolysis and fat utilization were observed, largely independent of the treatment effects.

No significant differences between treatments and between rates of work were demonstrated in these untrained hypertensive subjects. This conflicts with a number of studies that have reported attenuated lipolysis during therapy with β -adrenergic blockade.⁴⁻¹⁷ Unfortunately, most of these studies used exercise protocols that were considerably different from those used in the present study. The exercise protocols used previously generally fall into 1 of 4 categories: steady-state submaximal exercise^{15,16,18}; graded exercise tests where the work rate was increased at specified intervals either to exhaustion or to some fixed rate of work^{9,11}; a combination steady-state and graded exercise test to exhaustion^{4,5}; or exercise to exhaustion at a fixed heart rate or a fixed percent of $\dot{V}O_{2\max}$.^{6,7,12-14,17} It is well known that both intensity and duration of exercise greatly influence substrate utilization. Thus, differences in protocol must be considered when interpreting differences in results between studies. All but 4 of the studies cited^{6,7,15,16} used exercise intensities far in excess of those used in this study.

Lundborg et al⁷ reported reduced FFA release during prolonged submaximal exercise (50% of $\dot{V}O_{2\max}$) on a cycle ergometer to exhaustion with propranolol and placebo. Laustiola et al⁶ reported results similar to Lundborg et al,⁷ when normotensive men exercised at 50% of $\dot{V}O_{2\max}$ to exhaustion on a cycle ergometer. There are several possible reasons for the discrepancy between these studies and the data presented in this study. First, the average of the 2 exercise intensities used in the present study was slightly lower than those used in the 2 studies previously cited. Second, the hypertensive subjects in the present study were basically physically inactive with relatively low $\dot{V}O_{2\max}$ values (with several exceptions). Therefore, exercising at 25 and 45% of $\dot{V}O_{2\max}$ may not have been sufficient stimuli to increase lipolysis to a greater extent than could be provided during therapy with β -adrenergic blockade. Trained subjects rely more on FFA, and thus may be affected more.²⁰ Furthermore, the exercise bouts in the present study were terminated at 2 hours, whereas these other studies took their subjects to the state of exhaustion. In the studies of Hall¹⁵ and Gullestad¹⁶ and their co-workers, the duration of exercise was only 20 and 30 minutes, respectively, making comparisons with the present study difficult.

Trained subjects: FFA concentrations in the trained subjects increased linearly over time after 30 minutes of walking. No differences between rates of work were observed. Glycerol concentrations also increased over time, and respiratory exchange ratio values declined over time. These trends indirectly demonstrate an increased reliance on fat as a primary energy source over time despite a constant rate of work. Although the rate of

lipolysis did increase, attenuated lipolysis was observed with both pindolol and propranolol compared with placebo at 30 minutes of exercise. By 60 minutes of exercise, no differences between treatments were observed. Cleroux et al¹⁷ also reported an attenuation in the rate of increase in both FFA and glycerol values with β blockade during the first 30 minutes of exercise, after which time the rate of increase was similar to that for placebo conditions. Although no statistically significant differences existed, there was a tendency for plasma FFA and glycerol concentrations to be higher during placebo administration than during propranolol and pindolol administration. The respiratory exchange ratio values also tended to be lower with placebo than with propranolol and pindolol. During therapy with β -adrenergic blockade, lower FFA and glycerol levels and higher respiratory exchange ratio values than those during placebo therapy provide indirect evidence that lipolysis was attenuated. The present observation of a tendency to attenuate lipolysis with β -adrenergic blockade is in agreement with other studies conducted in both normotensive^{6,7,9-11,14-17} and hypertensive subjects.^{4,5,8,12,13} However, the ISA characteristic of pindolol was of no real benefit to these trained, normotensive subjects, since the degree of attenuation of lipolysis was not significantly different between pindolol and propranolol trials. Perhaps the ISA property in pindolol is not effective in endurance-trained subjects at these low rates of exercise. Because these persons have an increased ability to metabolize fat as a result of their training,²⁰ they may be more "sensitive" to blockade of their β -receptor sites. Martin et al²⁵ showed that adipocytes in humans have an increased sensitivity to catecholamines when endurance trained. Therefore, even the ISA property may not be as effective as it should in minimizing the degree that lipolysis is attenuated.

Although direct comparisons between these trained normotensive and untrained hypertensive subjects cannot be made, reasons for the differences observed between groups may be hypothesized. The trained subjects had lower respiratory exchange ratio values than the untrained subjects at rest and at 120 minutes of exercise. This indicates a greater reliance on β oxidation and fat metabolism. With β blockade, a tendency to attenuate lipolysis was not found in the untrained subjects. Perhaps the work rates performed by the untrained subjects did not require a greater delivery of FFA than could be supplied during therapy with β blockade; thus, no differences between treatments were observed. The trained subjects, however, by the nature of their training, had an increased ability to use fat. The rates of work they performed were much higher and may have required more FFA than could be supplied during therapy with β -adrenergic blockade; therefore, a tendency demonstrating differences between treatments was observed.

In line with this discussion, a number of the trained subjects had difficulty completing the 2-hour walk at 45% of their $\dot{V}O_2$ max, and 2 of the subjects were not able to complete >1 hour at this intensity. It is possible that either or both decreased lipolysis (intramuscular or

extramuscular) or alterations in potassium metabolism contributed to this difficulty at these higher rates of work.

Thus, it has been demonstrated that β -adrenergic blockade does not lower the rate of lipolysis in untrained hypertensive subjects when compared to similar trials administering placebo during exercise at 25 and 45% of $\dot{V}O_2$ max. It is important to note that these rates of work are more typical of the rates of work experienced by most persons who are prescribed β -blocking drugs. In trained normotensive subjects, although differences in FFA, glycerol and respiratory exchange values were not statistically significant when comparing the 3 treatments across all time periods, β blockade had a tendency to attenuate FFA and glycerol levels, when compared to placebo conditions. This provides indirect evidence that lipolysis was attenuated in these trained subjects. No direct benefit could be attributed to the ISA property. Finally, at these rates of work, lipolysis does not appear to be a limiting factor, and more than likely does not explain the fatigue experienced by most patients who are prescribed β -blocking drugs.

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Effects of Renin Inhibition in Systemic Hypertension

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The effect of the direct renin inhibitor enalkiren (Abbott Laboratories) was examined in 8 healthy patients with essential hypertension. With an unrestricted sodium diet, plasma renin concentration was inhibited within 10 minutes by intravenous enalkiren and remained essentially undetectable for ≥ 6 hours (11.9 ± 4 to 1.0 ± 0.6 ng angiotensin I/ml/hour, $p < 0.05$). Mean arterial blood pressure declined gradually (108 ± 5 to 84 ± 4 mm Hg, $p = 0.02$), as did plasma aldosterone concentration (14.4 ± 3.8 to 4.4 ± 0.8 ng/dl, $p = 0.03$), whereas plasma immunoreactive active renin concentration increased progressively (35 ± 14 to 160 ± 60 pg/ml, $p > 0.05$). Urinary excretion of the stable metabolite of prostacyclin (6-keto-prostaglandin $F_{1\alpha}$) decreased slightly, but not significantly (42 ± 10 to 33 ± 11 ng/g creatinine, $p = 0.13$). The addition of a diuretic decreased baseline blood pressure and increased baseline plasma renin and aldosterone values. Blood pressure responses to enalkiren were slightly (though not significantly) greater than those observed before diuretic administration. We conclude that enalkiren is effective in decreasing blood pressure and in inhibiting the renin system, without significantly altering urinary prostacyclin excretion, in patients with essential hypertension. These results suggest that the renin system contributes to the maintenance of elevated blood pressure in some patients with essential hypertension.

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Blockade of the renin-angiotensin aldosterone system with converting enzyme inhibitors is clinically effective in controlling blood pressure in many hypertensive patients, regardless of their baseline plasma renin activity.¹ However, the hypotensive effect of such drugs may be due to actions other than the blockade of angiotensin II production, because the inhibition of the converting enzyme may lead to decreased degradation of kinins and to stimulation of vasodilating prostaglandins,²⁻⁴ which also may contribute to the decrease in blood pressure in response to converting enzyme inhibitors. In contrast, renin carries out the first and rate-limiting step in the renin-angiotensin cascade and is known to have only 1 substrate, angiotensinogen. Therefore, renin inhibitors offer the advantage of providing specificity in determining the role of the renin system in hypertensive states.⁵

Enalkiren, a potent inhibitor of primate renin, acts as a substrate analog, mimicking the transition state of the renin-angiotensinogen complex.⁶ Previous studies in normotensive⁷ and hypertensive humans⁸⁻¹⁰ have demonstrated prolonged suppression of plasma renin activity (up to 24 hours) after a single drug dose, despite an estimated half-life of only 1.6 hours.⁷ In contrast, enalkiren administration has little effect on blood pressure in normotensive subjects,⁷ whereas its effect on blood pressure in hypertensive volunteers is variable.⁸⁻¹⁰ The present study was undertaken to determine the effect of renin inhibition on blood pressure, the renin system and urinary prostacyclin excretion in hypertensive subjects, in order to better define the role of the renin system in the maintenance of essential hypertension.

METHODS

Experimental protocol: Eight healthy patients with essential hypertension (Table I) stopped all medications and maintained an unrestricted sodium diet for 10 days as outpatients. The day before testing, patients were admitted to the General Clinical Research Center at Los Angeles County/University of Southern California Medical Center. The study was approved by the Human Research Committee and all subjects gave their written informed consent.

On the morning after admission, patients were kept fasting except for sips of water and placed in a seated position. Increasing intravenous doses of enalkiren (vehicle only, then 0.03, 0.1, 0.3 and 1.0 mg/kg) were administered at 45-minute intervals. Each dose was given over 5 minutes, using a 1.0 mg/ml solution. Blood pres-

sure was monitored automatically at 5-minute intervals by DINAMAP (Critikon, Tampa, Florida) from 30 minutes before the first dose until 2 hours after the last dose was given, with additional blood pressure measurements taken 4 and 6 hours after the last dose. Plasma renin concentration was measured at baseline, 10 and 45 minutes after each dose, and 2, 4 and 6 hours after the last drug dose. Plasma aldosterone concentration was measured at baseline and 45 minutes after each dose, and 2, 4 and 6 hours after the last drug dose. Four patients had plasma immunoreactive active renin measured at baseline, 45 minutes after each dose and 2 hours after the last dose. Four patients also had timed, matched urine collections for urinary prostacyclin collected in the afternoon of the day before testing and in the afternoon of the day of testing, with urine collection started immediately after the last drug dose.

To achieve salt depletion, patients were then placed on hydrochlorothiazide 25 mg orally twice a day for 7 days. Patients were then readmitted and the study was repeated.

Analytic procedures: All blood samples were collected into tubes containing EDTA, promptly centrifuged and stored at -20°C until assayed. Urine was promptly frozen at -20°C until assayed. Plasma renin concentration (which measures the enzymatic ability of plasma to generate angiotensin I [Ang I] in the presence of a non-limiting concentration of substrate) was determined as previously described in detail.¹¹ Plasma immunoreactive active renin concentration was determined using a novel immunoradiometric assay that uses an antibody directed against the active site of renin.¹² Plasma aldosterone was assayed by a specific radioimmunoassay.¹³ Urinary prostacyclin was determined by measuring the stable metabolite of prostacyclin (6-keto-prostaglandin F [PGF]_{1 α}) by a method previously described.¹⁴

Statistical analysis: Results are expressed as the mean \pm standard error of the mean. Normally distributed data were analyzed with the 2-tailed Student's *t*

TABLE I Clinical Data on Hypertensive Subjects

Age (yr) Race & Gender	Baseline Renin (ng Ang I/ ml/hr)	Baseline MAP (mm Hg)	Baseline Urinary Sodium (mg Na ⁺ / 24 hrs)	Maximal Decrease in BP (mm Hg)
22, O, M	33.7	92	85	20
24, W, M	23.3	100	136	40
33, H, M	6.4	109	32	32
40, B, F	4.6	121	152	17
49, B, M	5.8	126	30	34
50, B, M	12.3	99	216	20
56, W, F	23.3	98	111	26
41 \pm 5	11.9 \pm 4	108 \pm 4	113 \pm 22	31 \pm 5

Ang I = angiotensin I; B = black; BP = blood pressure; H = Hispanic; MAP = mean arterial pressure; O = oriental; W = white.

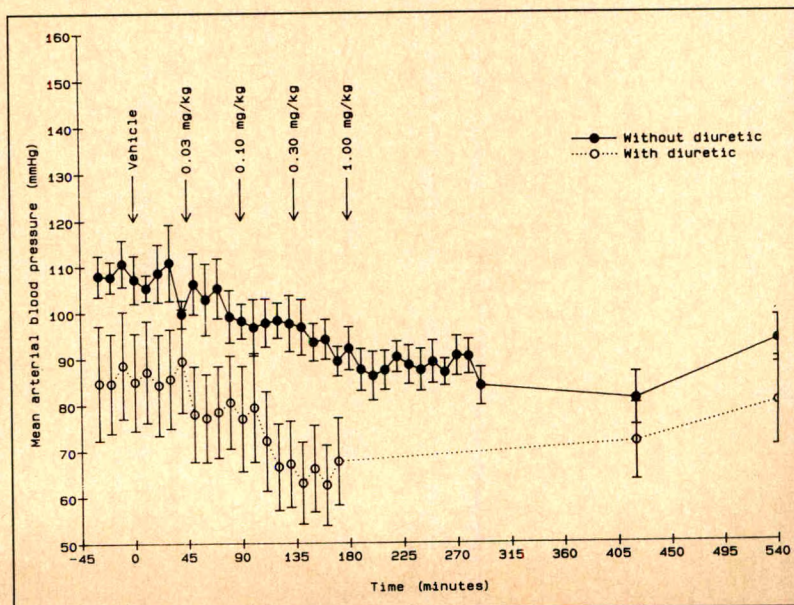
test for paired data, and abnormally distributed data were analyzed using the Wilcoxon signed rank tests. All statistical analysis and graph construction were performed with the assistance of the CLINFO VAX computer system.

RESULTS

Mean arterial blood pressure: Mean arterial blood pressure declined progressively as the dose of enalkiren was increased (108 ± 5 to 84 ± 4 mm Hg; Figure 1); this decrease was significant after the first dose ($p = 0.02$). Blood pressure continued to decrease after the drug was stopped; 4 hours after the last dose, it was 81 ± 6 mm Hg. Six hours after the last drug dose, it was still below baseline values (94 ± 5 mm Hg). There was no correlation between either baseline urinary sodium excretion or baseline plasma renin concentration and the maximal decrease in blood pressure that occurred in response to enalkiren (Table I).

After diuretic administration, blood pressure decreased; it also declined progressively in response to enalkiren (85 ± 11 to 57 ± 17 mm Hg; Figure 2). A

FIGURE 1. Response of mean arterial blood pressure to increasing doses of enalkiren in hypertensive patients studied without (closed bullets) or with (open bullets) diuretic twice a day for 1 week. Both groups show a significant, progressive decrease in blood pressure in response to enalkiren, although the diuretic-treated group had a lower starting mean arterial pressure and received only the vehicle,



significant decrease in blood pressure was again seen with the first dose ($p = 0.0001$). Because of the brisk response, the 2 largest doses (0.3 and 1.0 mg/kg) were not given. Four hours after the last dose, blood pressure had recovered somewhat (77 ± 14 mm Hg), but 6 hours after the last dose, it was still below baseline values (80 ± 10 mm Hg).

Plasma enzymatic activity of renin: Before diuretic treatment, plasma renin concentration fell to barely detectable levels 10 minutes after the smallest dose of enalkiren was administered (11.9 ± 4 to 1.0 ± 0.6 ng Ang I/ml/hour) and remained very low or undetectable (≤ 0.5 ng Ang I/ml/hour) for 6 hours after the last dose (Figure 2; $p < 0.05$).

After diuretic treatment, plasma renin was appropriately higher. However, it also decreased rapidly and significantly after the smallest dose of enalkiren ($28.6 \pm$

9.9 to 0.3 ± 0.3 ng Ang I/ml/hour) and remained undetectable (≤ 0.5 ng Ang I/ml/hour) 6 hours after the last dose (Figure 2; $p < 0.05$).

Plasma aldosterone concentration: Before diuretic treatment, plasma aldosterone decreased progressively in response to enalkiren (14.4 ± 3.8 to 4.4 ± 0.8 ng/dl); this decrease was significant after the first dose ($p = 0.03$). Six hours after the last dose, plasma aldosterone had increased to 11.3 ± 4 ng/dl, still below baseline values (Figure 3).

After diuretic treatment, plasma aldosterone was appropriately elevated (33 ± 5 ng/dl). In response to enalkiren, it decreased progressively to 20 ± 4 ng/dl; this decrease was significant after the second dose ($p = 0.02$). Six hours after the last dose, plasma aldosterone increased (21.6 ± 4.6 ng/dl), but was still below baseline values (Figure 3).

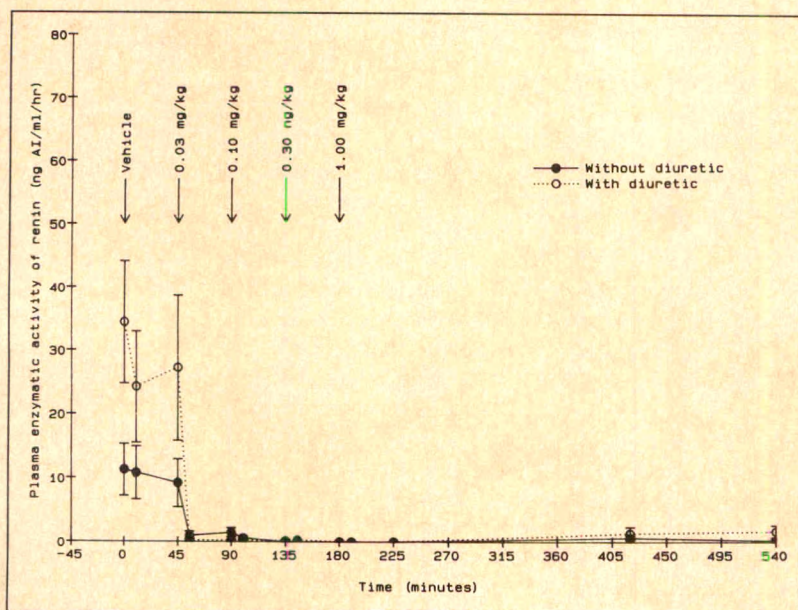


FIGURE 2. Response of plasma renin concentration to increasing doses of enalkiren in hypertensive patients studied without (closed bullets) or with (open bullets) diuretic twice a day for 1 week. There was rapid, complete and significant inhibition of renin with the first dose of enalkiren in both groups. Six hours after the last dose of drug, renin was still inhibited. When patients ingested diuretics, they had appropriately elevated renin, but suppression to virtually undetectable levels still occurred. AI = angiotensin I.

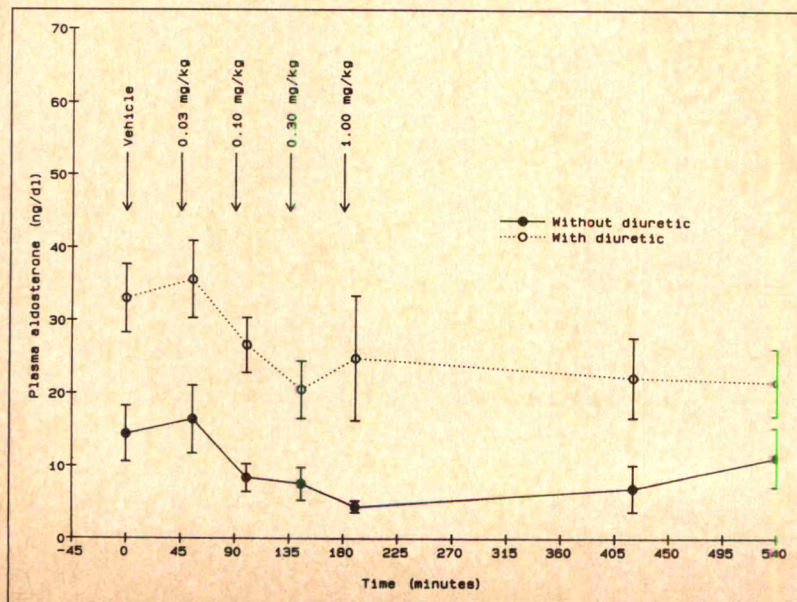


FIGURE 3. Response of plasma aldosterone concentration to increasing doses of enalkiren in hypertensive patients without (closed bullets) or with (open bullets) diuretic twice a day for 1 week. There was a modest but significant decrement in aldosterone in response to increasing doses of enalkiren. When ingesting diuretics, patients had appropriately elevated aldosterone and also had significant decreases in aldosterone in response to enalkiren.

Plasma immunoreactive renin: Before diuretic treatment, plasma immunoreactive active renin increased with enalkiren and continued to increase after the drug was discontinued (35 ± 14 to 160 ± 60 pg/ml). However, this increase was not significant, probably because

only a small number (4 patients) were sampled (Figure 4).

After diuretic treatment, plasma immunoreactive active renin was appropriately elevated (149 ± 44 pg/ml), increased in response to enalkiren, and continued to

FIGURE 4. Response of plasma immunoreactive active renin concentration to increasing concentrations of enalkiren in hypertensive patients studied without (*closed bullets*) or with (*open bullets*) diuretic twice a day for 1 week. There was a slow, insignificant increase in immunoreactive active renin in response to increasing doses of enalkiren in patients without diuretic. When patients ingested diuretics, they had higher baseline immunoreactive active renin, which increased significantly after the second dose.

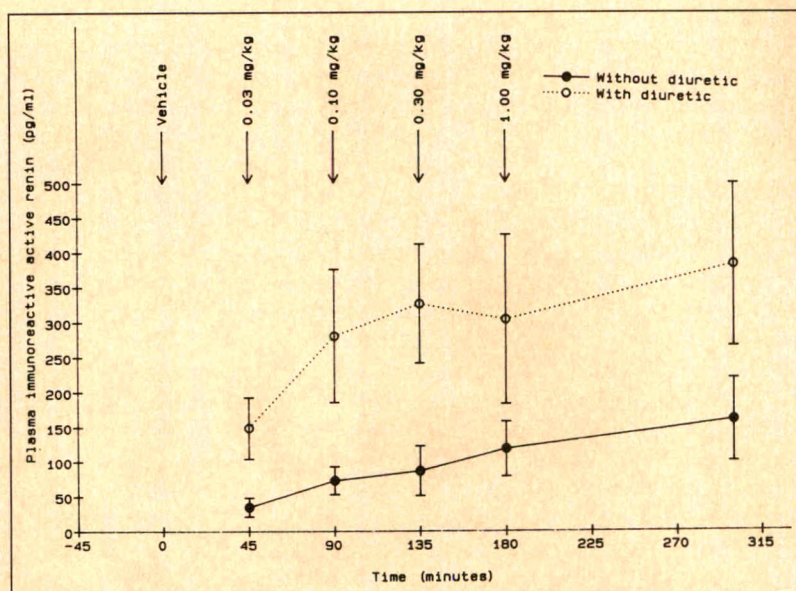
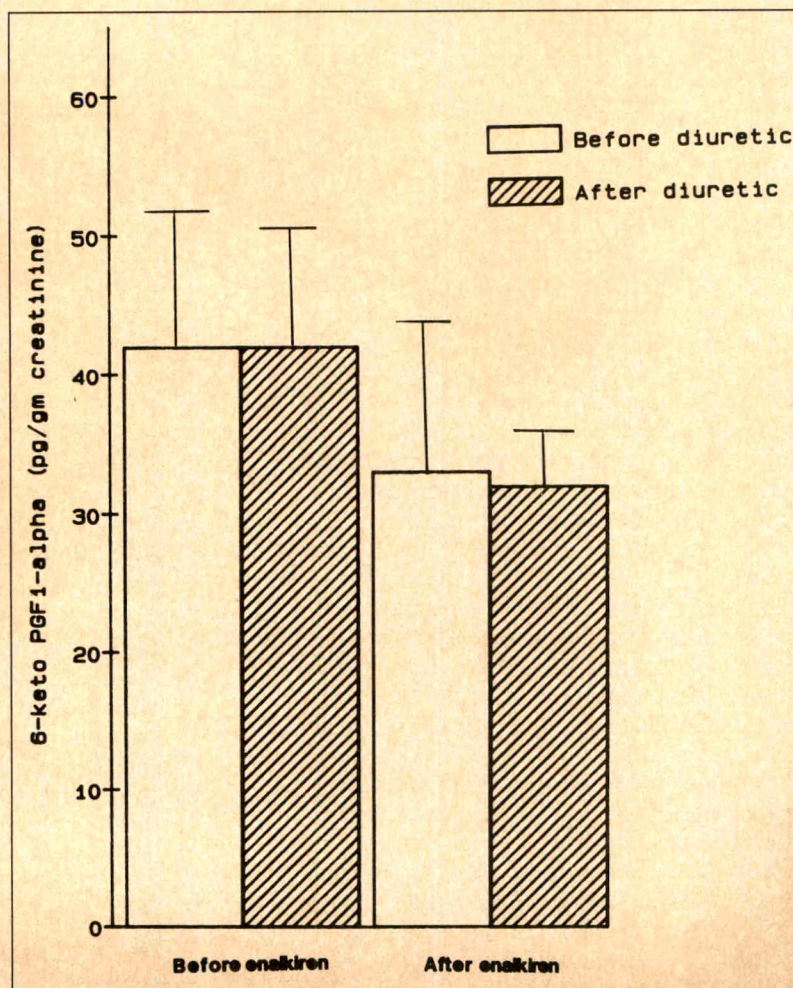


FIGURE 5. Response of the excretion of the stable metabolite of prostacyclin (6-keto-PGF_{1α}) in urine to enalkiren in hypertensive patients studied without (*open rectangle*) or with (*striped rectangle*) diuretic twice a day for 1 week. There was a slight but insignificant change in urinary 6-keto-PGF_{1α} excretion both before and after diuretic administration.



increase after the drug was stopped (up to 382 ± 117 pg/ml); this increase was significant after the second dose ($p = 0.02$).

Urinary prostacyclin: Before diuretic treatment, 6-keto-PGF_{1 α} excretion decreased slightly (42 ± 10 to 33 ± 11 pg/g creatinine) but not significantly after enalkiren ($p = 0.29$; Figure 5).

After diuretic treatment, 6-keto-PGF_{1 α} excretion again decreased slightly but not significantly in response to enalkiren (42 ± 8 to 32 ± 4 pg/g creatinine) ($p = 0.13$; Figure 5).

DISCUSSION

The present investigation demonstrates that the short-term administration of the renin inhibitor enalkiren inhibited the renin system and decreased blood pressure in 8 patients with essential hypertension. The duration of enalkiren's effects on the renin system and blood pressure were long-lasting, which is consistent with previous studies in human subjects.⁷⁻¹⁰ In contrast to converting enzyme inhibitors, enalkiren appears to have little effect on renal prostacyclin production. Thus, the major mechanism of action of enalkiren appears to be mediated through its effects on renin.

In previous studies of normotensive, salt-replete humans, a rapid decrease in plasma renin activity and plasma angiotensin II concentration was noted in response to enalkiren with no change in blood pressure.⁷ This lack of blood pressure reduction, despite suppressed plasma angiotensin II levels, is similar to that seen when normotensive volunteers are given converting enzyme inhibitors.¹⁴ In contrast, while our 8 hypertensive patients demonstrated rapid inhibition of plasma renin concentration, and a significant change in another parameter of the renin system, plasma aldosterone concentration, they also demonstrated consistent and significant decreases in blood pressure in response to enalkiren. This difference in blood pressure response occurred despite the fact that our patients received similar amounts of enalkiren and had similar average 24-hour urinary sodium excretion compared to the normotensive subjects in the aforementioned study. Reports by other investigators using enalkiren in hypertensive subjects have also noted rapid inhibition of plasma renin concentration. However, one study was unable to show a significant blood pressure reduction in hypertensive subjects using similar amounts of enalkiren to those used in the present study,⁸ whereas other investigators noted a clear-cut blood pressure response to increasing doses of enalkiren.^{9,10} Thus, in contrast to normal subjects, the renin system appears to contribute to the maintenance of elevated blood pressure in some patients with essential hypertension.

Of interest in the present study was the finding of no relation between the baseline urinary sodium excretion or the baseline plasma renin concentration and the total maximal decrease in blood pressure (Table I). A similar dissociation between baseline plasma renin activity and blood pressure response is often observed in hypertensive patients given converting enzyme inhibitors;¹⁵ patients with low baseline plasma renin activity may respond well to converting enzyme inhibitor administra-

tion.¹ That there is some relation between sodium status and degree of response to enalkiren is seen by the fact that the rate of blood pressure decline in patients receiving diuretics was slightly steeper than in salt-replete patients for the same dose of enalkiren; however, the slopes of the 2 lines are not significantly different.

The mechanism by which enalkiren decreases blood pressure may be more complex than inhibition of plasma renin. It has been suggested that the dissociation in time of the plasma renin activity and blood pressure response illustrates the relative importance of tissue renin systems, as opposed to plasma renin, in the maintenance of blood pressure¹⁶⁻¹⁹ and that the slow decrease in blood pressure might be explained by slow drug penetration into tissue. However, investigations in marmosets, using a different renin inhibitor, have demonstrated no tissue renin system inhibition 30 minutes after the drug was given despite inhibition of plasma renin and a significant decrease in blood pressure.²⁰ It is possible that reduction of blood pressure soon after the administration of a renin inhibitor may be due to the inhibition of circulating plasma renin activity; later reductions in blood pressure may be due to the inhibition of tissue renin systems.

Whether direct renin inhibition will prove to be more useful than converting enzyme inhibition remains to be determined. A therapeutic agent that affects the renin system alone may have advantages over converting enzyme inhibitors: (1) Because some of the adverse effects of converting enzyme inhibitors (e.g., cough and angio-neurotic edema) may be due to non-renin system effects of the drugs,⁵ therapy with agents that target only the renin system might alleviate some of these troubling side effects; (2) The effect of blood pressure reduction caused by converting enzyme inhibitors may be lost after long-term administration because of the reflex increase in plasma renin activity, which may allow generation of angiotensin II;²¹ (3) Studies at the tissue level in rats²² suggest that renin inhibitors and converting enzyme inhibitors may have different effects in the suppression of the local renin-angiotensin system.

Further clinical applications of renin inhibitors remain to be investigated, since converting enzyme inhibitors are currently used as first-line agents in the treatment of a number of human illnesses. Use of a direct renin inhibitor may help us elucidate the role of the renin system in the pathogenesis of these diseases.

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Importance of Hemodynamic Response to Therapy in Predicting Survival with Ejection Fraction $\leq 20\%$ Secondary to Ischemic or Nonischemic Dilated Cardiomyopathy

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To identify patients with left ventricular ejection fractions $\leq 20\%$ who are likely to survive on tailored medical therapy after referral to transplantation, this study of 152 patients addressed the hypotheses that (1) severely elevated filling pressures initially measured at referral would not necessarily predict poor outcome, (2) survival would be best when low pulmonary wedge pressures could be achieved with therapy tailored for hemodynamic goals, and (3) coronary artery disease would be an independent risk factor for early mortality. Despite an average initial ejection fraction of 0.15, cardiac index of 2.0 liters/min/m² and pulmonary artery wedge pressure of 28 mm Hg, the actuarial survival with tailored therapy was 63% at 1 year, with 34 of 41 (83%) deaths occurring suddenly. Survival was not related to initial filling pressure elevation, but was best predicted by the pulmonary artery wedge pressures during therapy; patients achieving pressure of ≤ 16 mm Hg had 1-year survival of 83 vs 38% ($p = 0.0001$). The other independent predictors were serum sodium and coronary artery disease. Patients with high filling pressures during therapy and coronary artery disease had 21% survival at 1 year. Survival after referral to transplantation with an ejection fraction $\leq 20\%$ is better than previously described. Patients in whom left ventricular filling pressures cannot be adequately reduced by tailored therapy, particularly if coronary artery disease is present, should be considered for early transplantation.

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Cardiac transplantation has been recommended to improve survival in patients with ejection fractions $\leq 20\%$.¹ However, the current shortage of donor hearts has created long waiting lists and it is necessary to identify potential candidates who are nonetheless likely to survive without early transplantation. Clinical factors predicting outcome in a heterogeneous population with ejection fractions $< 35\%$ ^{2,3} usually reflect decompensation and are thus unhelpful in patients referred for transplantation with an ejection fraction $\leq 20\%$. Prognosis has been compared to hemodynamic measurements at presentation,^{4,5} which in patients referred for transplantation may reflect more the vigor of previous therapy than the potential for survival on optimal therapy. Because most deaths occur early after evaluation, it would be useful to identify high- and low-risk groups at the time of discharge.

Despite previous therapy with vasodilators, digoxin and diuretics, most patients have severely elevated pulmonary artery wedge pressures at the time of referral to transplantation.⁶ Therapy tailored specifically to lower pulmonary artery wedge pressure minimizes ventricular volume and mitral regurgitation⁷ while maximizing cardiac output⁸ and improving clinical status,⁹ but it is not known whether the achievement of low filling pressures during therapy predicts subsequent outcome without transplantation. To address the following hypotheses, we compared survival without transplantation to the hemodynamic profile before and after therapy in 152 consecutive patients with ejection fractions $\leq 20\%$ who were discharged after evaluation for cardiac transplantation: (1) Severe initial elevation in pulmonary artery wedge pressure would not necessarily predict poor outcome; and (2) survival would be best in patients in whom the lowest pulmonary artery wedge pressure could subsequently be achieved. Because patients with heart failure due to coronary artery disease have the additional risks of reinfarction and primary reentrant ventricular tachyarrhythmias, we also hypothesized that (3) coronary artery disease would be an independent risk factor for higher mortality without transplantation.

METHODS

All adults referred for cardiac transplantation with a diagnosis of ischemic or nonischemic dilated cardiomy-

TABLE I Patients Referred for Transplantation with Ejection Fraction $\leq 20\%$: Clinical Characteristics

	All Patients (n = 152)	Coronary Artery Disease (n = 56)		Nonischemic Cardiomyopathy (n = 96)
Age (yrs)	45 \pm 13	52 \pm 9	*	41 \pm 13
Male/female	133/19	50/6		81/15
Ejection fraction	0.15 \pm 0.03	0.16 \pm 0.03	*	0.14 \pm 0.03
Duration symptoms of CHF (mos)	33 \pm 34	37 \pm 40		30 \pm 30
Previous vasodilator therapy	106/152 (70%)	34/56 (61%)		72/96 (75%)
Activity limitation [†]	3.3 \pm 0.7	3.2 \pm 0.6		3.3 \pm 0.7
Orthopnea [†]	2.7 \pm 1.2	2.5 \pm 1.3		2.9 \pm 1.2
Mean left ventricular end-diastolic diameter (mm)	77 \pm 10	76 \pm 11		77 \pm 10
Mean left atrial diameter (mm)	50 \pm 9	52 \pm 9		49 \pm 8
Mean serum sodium	135 \pm 6	134 \pm 6		135 \pm 6

* p < 0.05 difference between coronary artery disease and nonischemic cardiomyopathy.
[†] 0 to 4 scale (see Methods).
Values are expressed as mean \pm standard deviation.
CHF = congestive heart failure.

opathy underwent a standard procedure of evaluation and therapy since 1985. Patients >70 years of age or with a primary noncardiac medical condition felt itself to limit 1-year survival were excluded from this study. Coronary arteriography was performed, with coronary artery disease considered significant if a narrowing of $\geq 70\%$ in diameter had been documented in a major artery. Because all patients are between classes III and IV by New York Heart Association criteria, clinical status is measured more specifically on a 0 to 4 scale separately for activity limitation and orthopnea as previously described.¹⁰ Left ventricular ejection fraction was measured by radionuclide angiography or 2-dimensional echocardiography. This study included only patients with ejection fractions $\leq 20\%$.

Full transplant evaluation included measurement of pulmonary vascular resistance with a pulmonary artery flotation catheter, which was left in place in patients with pulmonary artery wedge pressure ≥ 20 mm Hg or a cardiac index ≤ 2.2 liters/min/m², or both. Hemodynamic measurements were repeated hourly for 2 to 4 hours without meals or change in prior medication. Thermodilution cardiac outputs were performed with iced solution in triplicate or until 3 readings agreed within 10%. Patients in whom hemodynamic parameters remained outside the criteria then discontinued previous medications and underwent tailored therapy, as previously described to minimize mitral regurgitation and maximize cardiac output.^{7,8} Intravenous nitroprusside and diuretics were titrated to approach the hemodynamic goals of pulmonary wedge pressure ≤ 15 mm Hg and systemic vascular resistance of $\leq 1,200$ dynes-cm⁻⁵ while maintaining systolic blood pressure at ≥ 80 mm Hg. After these goals were reached or after 48 hours had elapsed, oral vasodilators (captopril or hydralazine and isosorbide dinitrate) were added to maintain optimal hemodynamics during nitroprusside weaning. Digoxin therapy was maintained or begun unless there were specific contraindications.

Hemodynamics were measured during oral therapy after ≥ 4 dosing intervals before catheter removal.

(Baseline hemodynamics were also final hemodynamics in 15 patients in whom previous oral therapy was not altered.) Patients were then observed for 24 to 48 hours for initial adjustment of oral diuretics and potassium and for patient education regarding the flexible regimen of loop diuretics with intermittent metolazone to maintain weight within 2 pounds of discharge weight.

Transplantation was recommended to all patients who were eligible in terms of irreversible disease, recent history of severe symptoms and absence of major noncardiac illness.¹¹ After discharge, all patients were seen weekly until clinical stability was demonstrated,¹⁰ and thereafter every 2 to 12 weeks as needed.

Survival curves were calculated with the product-limit (Kaplan-Meier) estimate, using the BMDP statistical package,¹² candidates for transplantation were withdrawn at the time of transplantation. Survival was also recalculated including the 6 urgent transplants as deaths. Death was considered sudden if it occurred out of the hospital, during sleep or within 15 minutes of the onset of symptoms. Death during hospitalization for worsening congestive symptoms was considered a heart failure death.

Univariate analysis was performed using the baseline variables of age, presence of coronary artery disease, symptom duration, activity limitation, orthopnea, ejection fraction, echocardiographic left ventricular diameter, serum sodium, creatinine and blood urea nitrogen. Hemodynamic variables of heart rate, blood pressure, right atrial, pulmonary artery systolic and pulmonary wedge pressures, cardiac index, and systemic vascular resistance were included both from admission and after tailoring of therapy. Variables significant with a p value < 0.10 in univariate analysis were entered into the Cox proportional-hazards regression model, which retained all independent variables with a p value < 0.10.

To facilitate identification of high- and low-risk patients in a way that could be clinically useful, survival curves were compared for specific criteria. For continuous variables, survival was compared for patients divided into 2 groups according to population means for each

TABLE II Patients Referred for Transplantation with Ejection Fraction $\leq 20\%$: Hemodynamics Before and After Tailored Therapy

	All Patients (n = 152)		Coronary Artery Disease (n = 56)		Nonischemic Cardiomyopathy (n = 96)	
	Before	* After	Before	* After	Before	* After
Pressures						
Right atrium	13 \pm 7	7 \pm 4	13 \pm 7	7 \pm 4	13 \pm 7	7 \pm 4
Pulmonary artery systolic	55 \pm 16	42 \pm 12	60 \pm 16 [†]	45 \pm 14 [†]	53 \pm 15 [†]	41 \pm 10 [†]
Pulmonary artery wedge	28 \pm 9	17 \pm 6	28 \pm 8	18 \pm 6 [†]	28 \pm 9	16 \pm 6 [†]
Systemic arterial	85 \pm 11	76 \pm 10	85 \pm 10	77 \pm 9	84 \pm 12	76 \pm 10
Cardiac index (liters/min/m ²)	2.0 \pm 0.6	2.7 \pm 0.6	2.0 \pm 0.6	2.6 \pm 0.5 [†]	2.0 \pm 0.7	2.8 \pm 0.7 [†]
Systemic vascular resistance (dynes-s-cm ⁻⁵)	1,700 \pm 700	1,150 \pm 250	1,700 \pm 600	1,200 \pm 230 [†]	1,700 \pm 700	1,100 \pm 250 [†]
Heart rate (beats/min)	94 \pm 15	94 \pm 15	88 \pm 13 [†]	88 \pm 10 [†]	98 \pm 12 [†]	98 \pm 10 [†]

* Therapy caused significant differences in all parameters except heart rate.

[†] p < 0.05 difference between patients with coronary artery disease and patients with nonischemic cardiomyopathy.

Values are expressed as mean \pm standard deviation.

TABLE III Comparison of Patients with Successful Reduction of Elevated Pulmonary Artery Wedge (PAW) Pressures* to Patients with Persistent Elevation of PAW Pressures

	Successful Reduction of PAW Pressure (n = 61)	Persistent Elevation of PAW Pressure (n = 70)
At referral		
Right atrial pressure (mm Hg)	14 \pm 7	15 \pm 7
Pulmonary artery wedge pressure (mm Hg)	31 \pm 7	31 \pm 6
Cardiac index (liters/min/m ²)	1.9 \pm 0.7	1.9 \pm 0.6
Systemic vascular resistance (dynes-s-cm ⁻⁵)	1,700 \pm 600	1,750 \pm 700
On tailored therapy		
Pulmonary artery wedge pressure (mm Hg)	13 \pm 3	22 \pm 4
Right atrial pressure (mm Hg)	5 \pm 4	9 \pm 4
Cardiac index (liters/min/m ²)	2.8 \pm 0.7	2.5 \pm 0.5
Systemic vascular resistance (dynes-s-cm ⁻⁵)	1,100 \pm 230	1,200 \pm 280

* Excludes 21 patients with initial pulmonary artery wedge pressures ≤ 16 mm Hg.

[†] p < 0.05.

Values are expressed as mean \pm standard deviation.

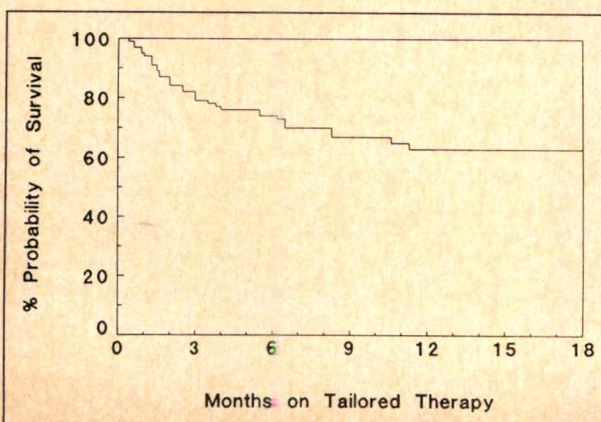
significant parameter. Differences between 2 curves were assessed with the Mantel-Cox statistic.¹² Group averages are expressed as mean \pm standard deviation.

RESULTS

The initial profile of the 152 patients (Table I) showed the average ejection fraction, cardiac index, pul-

monary artery wedge and right atrial pressures to be associated with poor prognosis for patients with heart failure.⁵ At the time of referral, 106 of 152 patients (70%) were already receiving vasodilators: converting enzyme inhibitors (n = 82), hydralazine (n = 22) or prazosin (n = 2). Tailored therapy decreased pulmonary wedge and right atrial pressures by 39 and 41%, with a simultaneous 49% increase in cardiac index and a 26% decrease in systemic vascular resistance (Table II). The average serum sodium (135 mEq/liter) did not change during the 24 to 72 hours between baseline and tailored therapy.

After discharge on tailored afterload reduction, actuarial survival was 73% at 3 months and 63% at 1 year (Figure 1). Death occurred suddenly out of the hospital in 34 of 41 (83%) deaths. Hospitalization for hemodynamic decompensation (symptomatic fluid retention, rising creatinine levels, or clinical evidence of resting hypoperfusion) resulted in death in 7 patients. Transplantation was performed in 43 of 152 patients, only 6 of whom showed clinical deterioration requiring hospitalization and a change to urgent status before transplantation. Recalculation including these 6 urgent transplantations as deaths yielded a survival of 61.6% at 1 year. For these 6 patients, the average pulmonary

**FIGURE 1.** Actuarial survival for 152 patients discharged on tailored therapy after referral for transplantation with ejection fractions $\leq 20\%$.

wedge pressure during therapy was 22 ± 5 mm Hg. The remainder of transplants were done without high priority in outpatients who were not different in any parameters from the remainder of the group.

Univariate analysis of age, symptom duration, activity limitation, orthopnea, left ventricular ejection fraction, left ventricular end-diastolic dimension, presence of coronary artery disease, serum sodium and baseline hemodynamics showed the only baseline predictors to be etiology ($p = 0.008$), serum sodium ($p = 0.014$) and cardiac index ($p = 0.024$). During tailored therapy, right- and left-sided filling pressures, cardiac index and systemic vascular resistance were predictive. Serum sodium did not change significantly during the 24 to 72 hours of therapy.

All variables significant from univariate analysis were included in multivariate analysis. The independent predictors of overall mortality were high final pulmonary artery wedge pressure during therapy ($p = 0.005$), low serum sodium ($p = 0.033$) and the presence of coronary artery disease ($p = 0.063$). Sudden death was predicted independently by the final pulmonary artery wedge pressure ($p = 0.009$) and the presence of coronary artery disease ($p = 0.076$).

To determine the clinical use of these predictors for individual patients, the likelihood of survival was com-

pared for groups above and below the average parameter value. When the final pulmonary wedge pressure was >16 mm Hg during tailored oral therapy, the probability of 1-year survival was 38% compared to 83% when the pressure could be reduced to ≤ 16 mm Hg ($p = 0.0001$). However, the initial pulmonary wedge pressure did not predict survival either in the Cox regression or when patients were grouped by initial pulmonary wedge pressure ≥ 28 mm Hg (57 vs 72% at 1 year, $p = 0.20$). Survival was also analyzed after excluding the 21 patients with an initial pulmonary wedge pressure ≤ 16 mm Hg who had a 95% 1-year survival; among the 131 patients with initial pressure >16 mm Hg, achievement of a final pressure ≤ 16 mm Hg identified a group with a 1-year survival of 79% compared to 33% ($p = 0.0012$) (Figure 2). Patients with initial pulmonary wedge pressures >16 mm Hg who could subsequently achieve lower pressures and better survival had the same baseline hemodynamics (average initial pulmonary wedge pressure 31 mm Hg) as patients who could not achieve final pressures ≤ 16 mm Hg (Table III).

In this population with ejection fractions $\leq 20\%$ due to coronary artery disease, mortality was twice as high as for patients with nonischemic cardiomyopathy (Figure 3). Sudden death accounted for 84% of mortality with coronary artery disease and 82% of mortality

FIGURE 2. Relation between survival and pulmonary artery wedge (PAW) pressure at baseline and on tailored therapy in 152 patients discharged after referral for cardiac transplantation with ejection fractions $\leq 20\%$.

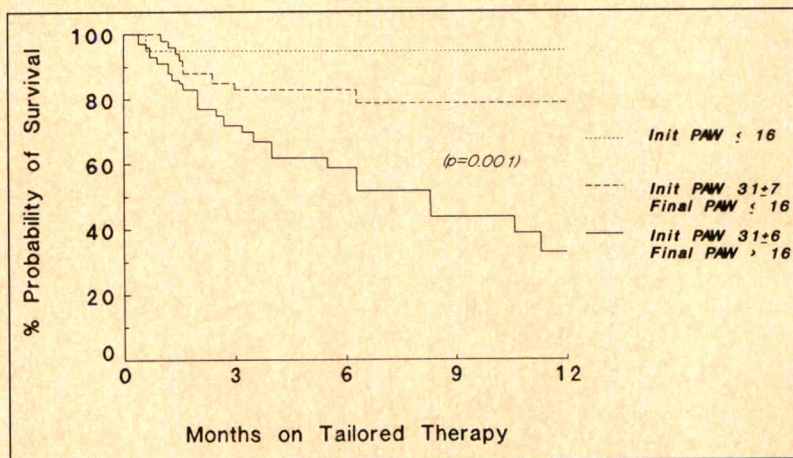
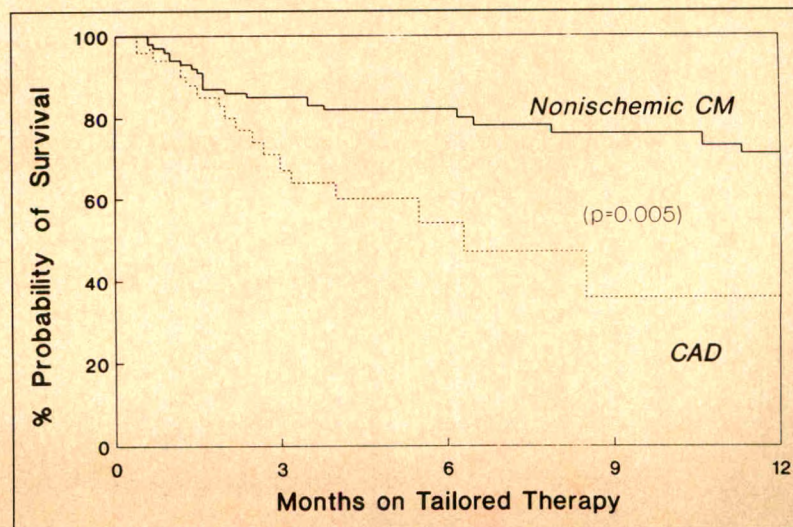


FIGURE 3. Relation between the presence of coronary artery disease (CAD) and survival in 152 patients discharged on tailored therapy after referral for cardiac transplantation with ejection fraction $\leq 20\%$. CM = cardiomyopathy.



with nonischemic cardiomyopathy. Compared to patients with nonischemic cardiomyopathy (Tables I and II), patients with coronary artery disease were older and had higher ejection fractions. After therapy tailored to hemodynamic goals, the pulmonary artery wedge and pulmonary artery systolic pressures and systemic vascular resistance were higher, and heart rate and cardiac index lower (Table II). The final pulmonary artery wedge pressure was >16 mm Hg in 33 of 56 (59%) patients with coronary artery disease compared to 40 of 96 (42%) patients with nonischemic cardiomyopathy ($p < 0.05$).

Although patients with coronary artery disease had slightly worse hemodynamic profiles during therapy, multivariate regression showed coronary artery disease to increase mortality independently. Actuarial curves with both risk factors showed patients achieving a low final pulmonary artery wedge pressure to have good survival regardless of etiology (Figure 4). However, patients with coronary artery disease were not only more likely to maintain elevated pressures despite therapy, but they also were at higher risk with these filling pressures than patients with nonischemic cardiomyopathy ($p = 0.05$).

Although reflecting a trend toward worse outcome, the serum sodium of 135 mEq/liter (average for the population) was not very useful in identifying high-risk patients in this advanced heart failure population. Survival was 59% at 1 year for patients with serum sodium ≤ 135 mEq/liter compared to 66% for those with higher serum sodium levels (difference not significant).

Right atrial pressure when initially >13 mm Hg did not predict mortality (62 vs 63%), but when it was >7 mm Hg during therapy it was associated with 50% 1-year survival compared to 71% ($p = 0.009$). The pulmonary artery systolic pressure was shown to be equivalent to pulmonary artery wedge pressure during therapy for predicting both total and sudden death. Initial cardiac

index ≤ 2.0 liters/min/ m^2 separated groups with survival probability of 53 vs 71% ($p = 0.03$). However, the final cardiac index was no more useful than the baseline value for group separation (57% survival when ≤ 2.7 liters/min/ m^2 , compared with 67% [$p = 0.20$]).

DISCUSSION

This study focused on patients with ejection fractions $\leq 20\%$ who were discharged after referral for transplantation. Unlike other heart failure populations,²⁻⁵ survival was not predicted by the severity of hemodynamic compromise at referral, but was predicted by the success of therapy designed to lower pulmonary artery wedge pressure. Patients with coronary artery disease had a slightly poorer response to therapy but an independently increased risk of death. Despite the initial poor status of the whole group, survival without transplantation was 63% at 1 year.

Ventricular filling pressures and survival: Elevated ventricular filling pressures at baseline have predicted survival in patients with a wide spectrum of disease severity and various subsequent therapies.^{4,5} In our population, the 14% of patients with normal initial filling pressures had a 1-year survival rate of 95%. However, for the remaining 86% of patients, who initially had high pressures, the degree of baseline elevation did not correlate with survival; instead, survival was predicted by the success of therapy tailored specifically to reduce pulmonary wedge pressure.

Studies in which early hemodynamic responses to therapy did not predict outcome¹³⁻¹⁵ have defined responses by the changes in forward output or mean arterial pressures (which were not predictive in our study either), or by percent change in hemodynamic parameters rather than the achievement of absolute hemodynamic goals. In addition, effective maintenance of early stabilization requires vigilant control of fluid balance after discharge, which is difficult if patients cannot man-

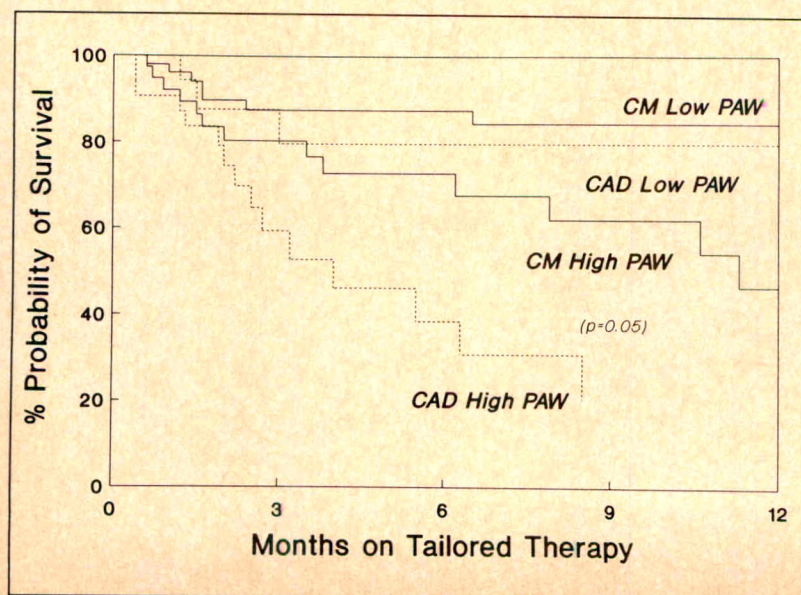


FIGURE 4. Relation between presence of coronary artery disease (CAD), pulmonary artery wedge (PAW) pressures during tailored therapy, and survival in 152 patients discharged after referral for cardiac transplantation with ejection fractions $\leq 20\%$. CM = cardiomyopathy.

age a flexible diuretic regimen and return for frequent follow-up care.

It is not known whether achieving low filling pressures with vasodilators and diuretics alone creates survivors or merely identifies survivors. Both the hydralazine/isosorbide dinitrate combination and enalapril improved survival when adjusted empirically in patients with less severe heart failure.^{3,16} Clinical status has been improved and there are fewer rehospitalizations after therapy tailored to hemodynamic goals in patients who, at referral, were severely compromised despite previous empiric vasodilator therapy.^{8,10} The associated reductions in ventricular volume and atrioventricular valve regurgitation⁷ may contribute not only to improved symptomatic status,¹⁷ but also to decreased wall stress and myocardial oxygen requirements during the subsequent year. Alternatively, patients achieving low ventricular filling pressures may have intrinsically less decompensation. If so, tailored therapy is effective in selecting these patients from a population who by usual criteria at the time of referral have a poor prognosis.²⁻⁵

The relation between irreducibly elevated filling pressures and sudden death is not understood. Extensive myocyte loss and fibrosis may reduce compliance and form the substrate for reentrant arrhythmias. Volume reduction can be limited by intense neurohumoral stimulation, which may aggravate tachyarrhythmias.¹⁸ Sudden death in this population can result also from bradyarrhythmias,¹⁹ which may be provoked by reflex abnormalities in advanced heart failure, predisposing patients to vasodepressor syncope.²⁰ Such reflexes may be more easily triggered when the wall tension in dilated ventricles is further increased by high filling pressures.

Coronary artery disease and survival: Coronary artery disease has been shown to limit survival with heart failure in some studies,^{3,4,21} but not in others, and has not been assessed independently of hemodynamic predictors. Patients with previous myocardial infarction receive more intense surveillance and may be referred earlier, with higher ejection fraction and lower volumes.²² Once the ejection fraction is $\leq 20\%$, those with coronary artery disease appear to have not only a worse hemodynamic response to therapy, but also an additional independent risk for both total mortality and sudden death.

Autopsy studies have shown reinfarction to be a major cause of mortality after previous myocardial infarction.²³ In addition, patients with heart failure and prior infarction are more likely to have the substrate for reentrant ventricular tachyarrhythmias.²⁴ The higher death rate in patients with both coronary artery disease and heart failure reflects the combined risks for sudden death in general heart failure and those risks specifically associated with coronary artery disease.

Study limitations: The survival data are influenced by the possibility of transplantation. With current priority systems, all outpatients are ordered only by time on the waiting list, so there is no reason why those receiving a heart early would have been at higher risk for early mortality. Of the 152 patients, clinical deterioration requiring hospitalization and higher priority be-

tween discharge and transplantation occurred in only 6, whose average pulmonary wedge pressure during therapy was 22 mm Hg, so their inclusion as end points would only have increased the apparent discriminating power of the response to therapy. The overall survival at 1 year was only reduced from 63 to 61.6% when these urgent transplantations were equated with death. The 37 outpatients undergoing transplantation had no differences in measured parameters from the patients continuing to receive tailored therapy. The similarity between outpatients awaiting transplantation and those continuing to receive medical therapy after referral for transplantation has been demonstrated previously.¹⁰

This study focused on variables that could be measured at referral and improved with therapy before discharge. There were no systematic evaluations of 24-hour electrocardiographic recordings, exercise capacity or serum catecholamine levels, which have been predictive in some populations.^{21,25,26}

Implications of survival with ejection fraction $\leq 20\%$: The 63% survival demonstrated without transplantation is greater than previously expected for patients with this profile (Table I). Ejection fraction $\leq 20\%$, severe clinical compromise, cardiac index < 2.25 liters/min/m², pulmonary artery wedge pressures > 25 to 27 mm Hg, and right atrial pressures > 10 mm Hg have all been associated with 1-year survivals of $< 40\%$.^{4,5,21,25} Survival for many of these patients may have been influenced either by experimental protocols or the lack of systematic outpatient follow-up after initial evaluation. When predicting survival with and without transplantation, it is essential to recognize also that patients with advanced age and other major medical problems are often included in medical studies, but are excluded from the population acceptable for transplantation.

Transplantation has been recommended for patients with ejection fraction $\leq 20\%$, even in the absence of coronary artery disease.¹ The overall survival in this study of 63% at 1 year with tailored therapy is much lower than the 80 to 90% seen after transplantation.²⁷ However, patients who could achieve low pulmonary wedge pressures had a survival of 83% without transplantation. Moreover, patients surviving on tailored therapy frequently achieve functional capacity equivalent to that after transplantation.¹⁰ Thus, patients achieving a low pulmonary wedge pressure should have lower priority for transplantation, which is currently severely limited by the shortage of donor hearts²⁸ such that twice as many patients are listed each month as actually receive transplantation.²⁹ Patients with persistent high filling pressures, particularly in the presence of coronary artery disease, should be considered for early transplantation. Improvement in our ability to predict and prevent sudden death,³⁰ which was responsible for 83% of the mortality in this discharged population, might allow even more patients to defer or avoid transplantation.

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Use of Auscultation to Follow Patients with Mitral Systolic Clicks and Murmurs

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Mitral systolic clicks and murmurs together with associated symptoms constitute a major reason for cardiologic referral. Although echocardiography with Doppler study enables characterization of the mitral valve apparatus and quantification of regurgitation, its use has resulted in an overemphasis of the technical diagnosis of mitral valve prolapse and an undervaluation of diagnosis based on physical examination. To determine the clinical significance of an auscultatory classification of mitral systolic clicks with or without precordial systolic murmurs, 1 consultant's medical records of 291 patients with these signs were reviewed. Based on initial auscultatory findings, patients were divided into: (1) single or multiple apical systolic clicks with no murmur (n = 99); (2) single or multiple apical systolic clicks and a late systolic murmur (n = 129); and (3) single or multiple apical clicks and an apical pansystolic murmur or murmur beginning in the first half of systole (n = 63).

The average duration of patient follow-up was 8 years (range 1 to 30). The prognosis was excellent for patients from all 3 classes. Two cardiac-related deaths occurred: 1 each from classes 1 and 2. Mitral valve surgery was performed in 3 class 2 patients (2%) and in 2 class 3 patients (3%). No patient developed endocarditis during follow-up. Palpitations, with varying anxiety overlay, constituted a major indication for cardiologic referral in all 3 classes. Auscultatory findings were valuable to the physician for explanation and relief of patient anxiety. For patient management, use of an auscultatory classification may be preferable to the technically generated term "mitral valve prolapse."

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During the last 20 years echocardiography has popularized the diagnosis of mitral valve prolapse. However, the wealth of information available from M-mode, 2-dimensional and Doppler echocardiographic examination has not necessarily resulted in improved patient management. Instead, the uncertainty engendered in the physician by the profusion of information on mitral valve prolapse may be transmitted to the patient, whose presenting symptomatology is often overlaid with anxiety. The cardiologist may be misled when extrapolating to the office practice prognostic data from hospital echocardiography laboratories, surgical case examinations, postmortem examinations, or epidemiologic studies of normal populations.¹⁻⁷ Furthermore, mitral valve prolapse frequently occurs in the absence of auscultatory findings, whereas, conversely, auscultatory findings are present in the absence of echocardiographic abnormality.⁸

The popularity of echocardiography has resulted in less emphasis being placed on auscultatory findings. However, the management of these patients, whose varied presentation is often overlaid by anxiety, may be improved more by clinical examination and judgment rather than by a reliance on expensive technology.

To determine the usefulness of a classification based on auscultatory criteria, we studied the clinical course of 291 patients, referred to 1 cardiologist (OBT) for a variety of signs and symptoms, in whom combinations of nonejection clicks and systolic murmurs consistent with mitral regurgitation were present. Echocardiography was performed, when available, to determine the relation between the auscultatory and echocardiographic findings.

METHODS

A retrospective analysis was made of the medical records of all patients seen between 1958 and 1988 in 1 consultant's cardiology practice (OBT). Patients included in the study were the 291 in whom a diagnosis of clicky mitral valve was made.

Classification based on auscultation: Auscultation was performed with the patient in the supine, left lateral, seated and standing positions, before and after mild sit-up exercise. The patients were divided into 3 classes, depending on the auscultatory findings during the initial examination.

Class 1 comprised patients with mid-to-late apical systolic click or clicks with no murmur (n = 99; 68 women, 31 men). Class 2 comprised patients with mid-to-late apical systolic click or clicks with a late systolic murmur, either constant or variable (n = 129; 89 wom-

TABLE I Age and Gender Distribution

Class 1							
Age (yr)	<20	20-29	30-39	40-49	50-59	60-69	70-79
Women (n)	5	20	17	15	11	5	1
Men (n)	1	3	11	5	3	0	2
Class 2							
Age (yr)	<20	20-29	30-39	40-49	50-59	60-69	70-79
Women (n)	9	18	18	13	13	7	1
Men (n)	4	6	19	4	8	7	1
Class 3							
Age (yr)	<20	20-29	30-39	40-49	50-59	60-69	70-79
Women (n)	5	6	12	4	8	3	1
Men (n)	0	2	4	4	7	5	2

en, 40 men). Class 3 comprised patients with mid-to-late apical systolic click or clicks with a pansystolic murmur or apical systolic murmur beginning in the first half of systole and ending with the second heart sound (n = 63; 39 women, 24 men).

Phonocardiograms were recorded in 25% of cases. In 4 patients included in the study, the phonocardiogram documented a nonejection click, whereas, on auscultation, the click could not be definitely distinguished from the onset of the systolic murmur. In all 4 patients, the nonejection click was associated with a late systolic murmur that began abruptly.

Subjects excluded: Thirty patients with apical pansystolic murmurs, whose echocardiograms showed classic prolapse, were excluded because no click was heard or demonstrated on phonocardiography. Also excluded were patients with late systolic murmurs that did not begin abruptly and that were not associated with a click. When echocardiography became available, none of any similar subsequent patients had echocardiographic evidence of prolapse.

Echocardiography: Echocardiography was performed as part of the initial consultation in 50% of cases: M-mode echocardiography in 25% and M-mode with 2-dimensional echocardiography, when it became available, in 25%. Mitral valve prolapse was classified (by OBT) as definite, possible or absent at the time of echocardiography. The extent of prolapse was measured as the number of millimeters below the CD line in the longitudinal parasternal view.⁷

Follow-up: Follow-up was obtained in 98% of patients. It consisted of repeat consultation in 33% and telephone contact with detailed questioning regarding symptoms and treatment in 27%. Vital status alone was obtained in 38% of patients with the assistance of the Department of Public Health of Western Australia. It was ascertained that none of the latter group had had cardiac surgery. Three percent were found to have died from noncardiac causes. Two percent were lost to follow-up. Mean duration of follow-up was 8 years.

RESULTS

Age and gender distribution: There was a predominance of women in the study, particularly in the younger age group (Table I). Women comprised 75% of pa-

TABLE II Primary Presenting Sign or Symptom

	Class 1 (n = 99)	Class 2 (n = 129)	Class 3 (n = 63)
Click ± Murmur (%)	29 (29)	43 (35)	24 (38)
Palpitations			
Excluding paroxysmal tachycardia (%)	23 (23)	39 (30)	9 (15)
Including paroxysmal tachycardia (%)	14 (14)	6 (5)	3 (5)
Chest Pain (%)	17 (17)	19 (15)	13 (20)
Dyspnea (%)	7 (7)	12 (11)	10 (16)
Syncope (%)	6 (6)	6 (5)	2 (3)
Exhaustion (%)	3 (3)	4 (3)	2 (3)

tients <50 years and 55% of patients ≥50 years. This age and gender distribution was similar in the 3 classes.

Etiology: An immediate family history of mitral valve abnormality was obtained in only 6 patients.⁹ Seven had a history of rheumatic fever. In 2 patients, the onset of a click and murmur together with echocardiographic prolapse was later attributed to an episode of myocarditis; the auscultatory signs and echocardiographic evidence of prolapse disappeared within 4 months. Two patients had midsystolic clicks and late systolic murmurs, without echocardiographic evidence of prolapse, after inferior myocardial infarction. In both instances the clicks disappeared within 5 years.

Presenting sign or symptom: There were multiple indications for referral in 40% of patients, but only the primary sign or symptom that prompted referral to the cardiologist is listed in Table II. Palpitations constituted a major presenting symptom in all groups. The symptoms were similar in all classes, with a trend for dyspnea to be seen more frequently in class 3, compared with classes 1 and 2. The sudden onset of dyspnea or chest pain, suggestive of rupture of mitral valve chordae,¹⁰ prompted the initial referral in 3% of patients from class 1, 6% from class 2 and 8% from class 3.

Clinical course: Of those reexamined during follow-up, a late systolic murmur developed in 19% (5 of 26) of class 1 patients, and progressive regurgitation occurred in 7% (3 of 43) of class 2 patients and in 8% (2 of 25) of class 3 patients. Mitral valve surgery in the form of reconstruction (n = 3) or replacement (n = 2) was performed in 3 patients from class 2 (3%) and in 2 (3%) from class 3 (Table III). In all cases the primary indication for surgery was disabling dyspnea despite medical therapy. It is of note that 5 of the 30 patients with pansystolic murmurs and echocardiographic evidence of prolapse, excluded from the study because of the absence of a click, required mitral valve surgery over the average 8-year follow-up period.

Endocarditis: During follow-up, no patient developed endocarditis; however, 2 class 2 patients had a previous history of endocarditis.

Cerebral complications: No patient had confirmed cerebral embolism.

Arrhythmias: Palpitations were the main indication for medical treatment and were a source of anxiety for patients in all classes. A variety of antiarrhythmic agents, primarily β blockers, was successfully used, almost always prescribed by the referring doctor. Four of

5 patients with exercise-induced palpitations were successfully treated by a small dose of β blocker 2 hours before exertion. Arrhythmias corresponding to patient symptoms were documented in 10% of cases at the time of physical examination, and were predominantly isolated ventricular premature beats.

During follow up, an antiarrhythmic agent was taken either consistently or intermittently by 39% of patients from class 1, 35% from class 2 and 27% from class 3. The onset of atrial fibrillation caused cardiac decompensation, which prompted mitral valve surgery in 3 of the 5 patients requiring surgery.

Mortality: One probable arrhythmic death occurred in a 37-year-old woman with a click and a late systolic murmur (class 2) who was found dead in bed. Nine years previously her electrocardiogram showed both atrial and ventricular extrasystoles, which disappeared with exercise. At the time of death she was taking no antiarrhythmic therapy. Postmortem examination revealed widespread patchy myocardial fibrosis, no evidence of coronary artery disease and a normal mitral valve. A class 1 patient died of complications of pulmonary fibrosis after chronic use of amiodarone for paroxysmal atrial flutter.

Echocardiography: In those examined by echocardiography, definite mitral valve prolapse was present in 50% of class 1, 72% of class 2 and 74% of class 3 patients (Table IV). Echocardiography was technically inadequate in 4 cases. In patients with confirmed prolapse, mean posterior displacement was 3.5 ± 1.5 mm in class 1, 5.0 ± 1.9 mm in class 2, and 6.0 ± 2.6 mm in class 3. The differences in posterior displacement between classes 1 and 2, and between classes 1 and 3, were significant ($p < 0.05$ by analysis of variance post hoc Neuman-Keuls multiple range test). Leaflet thickness > 5 mm was seen in 1 class 2 patient and in 2 patients from class 3. The patient from class 2 required mitral valve surgery.

DISCUSSION

This study indicates a good prognosis for patients with nonejection clicks, with or without mitral systolic murmurs, referred to a consulting cardiology practice. The auscultatory classification aided in identification of patients, exclusively from class 2 or 3, at slightly increased risk of developing severe mitral regurgitation requiring surgery.

Because most studies suffer from some degree of selection bias, their conclusions can be best applied to patients with similar inclusion criteria. This study is relevant to patients referred to a cardiologist by a referring physician, perhaps the most common scenario. The freedom from clinical complications in this study is in marked contrast to those noted in data from patients referred for echocardiographic examination in a major tertiary institution.⁴

Patients with single or multiple nonejection clicks in the absence of a murmur (class 1) have an excellent clinical outcome, with freedom from severe mitral regurgitation, requirement for surgery, or endocarditis. Nineteen percent of these patients developed a late systolic murmur on follow-up examination. Patients with

TABLE III Clinical Course

Class	No. of Pts.	Mitral Valve Surgery	Infective Endocarditis	Cardiac-Related Death
1	99	0	0	1 (1%)
2	129	3 (2%)	0	1 (1%)
3	63	2 (3%)	0	0

TABLE IV Echocardiographic Features

Class	Definite Prolapse (%)	Suggestive Features/ No Definite Prolapse (%)	Normal (%)	Technically Unsatisfactory (%)
1	50	24	26	0
2	72	13	13	4
3	74	14	11	0

nonejection clicks and murmurs beginning in the second half of systole (class 2) or with long systolic murmurs associated with a click (class 3) are at slightly increased risk of developing severe mitral regurgitation and requiring mitral valve surgery (approximately 3% over an 8-year period). Mitral valve surgery in this population was determined mainly by patient symptoms.

The frequency of arrhythmias and the difficulty of arrhythmia management are reported to be more likely related to the severity of mitral regurgitation than to echocardiographic findings.^{7,11} In 1 patient in the present study, preoperative paroxysmal ventricular tachycardia disappeared after mitral valve surgery. However, 1 class 2 patient with a history of documented atrial and ventricular premature beats suppressed by exercise presumably died from a sudden arrhythmia.

No endocarditis occurred during follow-up. Details of the use of antibiotics, which were prescribed by the primary physician, were not documented. However, prophylaxis was recommended for all groups.^{12,13}

Anxiety associated with palpitations and the diagnosis of cardiac disease was a major problem in patient management in all classes. The good prognosis of all groups enables the physician to focus on attempts to decrease the frequency of arrhythmia and to alleviate the anxiety often associated with a mysterious diagnosis of prolapse. Experience has shown that it is much easier for patients to understand that their valve, which is designed to function without a noise, is making a clicky noise, than it is for them to grasp the subtleties of mitral valve movement inherent in the term prolapse. Phonocardiography, a neglected art, provides documentary evidence for the doctor, who can explain it easily to the patient and their family, who are thereby reassured. Because cardiology review is often for patient reassurance, particularly for patients from class 1, the time period between reviews may depend primarily on the cardiologist's assessment of how often such reassurance is warranted. Alleviation of anxiety helps significantly in arrhythmia control and may be of the utmost importance in patients who are suspected of dysautonomia.¹⁴

In this low-risk population, it is difficult for echocardiography to provide an incremental advantage in prog-

nostic assessment to the auscultation-based classification. Furthermore, timing of surgery in this and other series is based primarily on symptoms. Before surgery, echocardiography provides a measure of left ventricular function and is valuable in deciding whether valve reconstruction is possible. In this study, echocardiography did not reveal any unsuspected anatomic diagnosis. The echocardiographic extent of prolapse related to the auscultatory class. Thus, class 1 was associated with a smaller extent of prolapse than either class 2 or 3. In the present study, prolapse was not detected in 25% of patients with clicky mitral valves. Basing a clinical diagnosis on echocardiographic criteria is therefore unsatisfactory, particularly as there is disagreement regarding echocardiographic classification.¹⁵⁻¹⁸ It is of note that 5 of the 30 subjects with pansystolic murmurs, who had echocardiographic prolapse but who were excluded from the study because of the absence of a click, required surgery during the follow-up period. Thus, the absence of a click with a pansystolic murmur in association with mitral valve prolapse may indicate a population at increased risk of severe mitral regurgitation.

Leaflet thickening, which qualified as "classic prolapse," was present in 2% of class 2, in 3% of class 3, and in none of class 1 patients. Patients with classic prolapse had moderately severe mitral regurgitation.

Auscultation versus echocardiography in patient management: Identification of patients at slightly increased risk of severe mitral regurgitation requiring surgery is provided both by auscultation and by echocardiography. Because current indications for mitral valve surgery are based primarily on symptoms, the prospective identification of patients at increased risk may not have a major effect on altering patient management, although it will enable the physician to review such a patient more frequently. The use of an auscultatory rather than echocardiographic classification offers several advantages for patient management. In contrast to echocardiography, auscultatory data can be readily and quickly acquired by the physician at the first visit with a stethoscope, can be easily repeated, can be readily presented by the physician and understood by the patient and does not involve additional cost.

The ready acceptance of the echocardiographic finding of prolapse as a clinical diagnosis reflects the homage we pay to technology. Because the echocardiographic findings can sometimes be in doubt, and because the clinical outcome is related to symptoms and to

auscultatory findings, an auscultatory classification based on the presence of mitral systolic clicks with or without a murmur may be preferable.

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Quantitative Analysis of Ventricular Late Potentials in Healthy Subjects

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Signal averaging is a technique that improves the signal-to-noise ratio. Obscuring random noise, it allows the detection of low-amplitude wave forms in the terminal portion of the QRS complex, also known as ventricular late potentials. A higher incidence of arrhythmic events has been found in patients with abnormal ventricular late potentials after an acute myocardial infarction. Few studies have been conducted in healthy subjects to assess normal values. Sixty-one healthy subjects were enrolled in our study (33 men and 28 women). The results (mean \pm standard deviation) are as follows: duration of the filtered QRS (QRS duration) was 95 ± 10 ms; duration of the low-amplitude signals in the terminal portion of QRS $<40 \mu\text{V}$ (LAS <40) was 32 ± 8 ms; and root-mean-square voltage in the last 40 ms (RMS-40) was $33 \pm 16 \mu\text{V}$. A significant difference was noted in QRS duration between men and women (98 ± 11 vs 92 ± 6 ms, $p = 0.006$); no difference was found in LAS <40 (31 ± 8 vs 34 ± 8 ms) and in RMS-40 (36 ± 17 vs $30 \pm 13 \mu\text{V}$). QRS duration confidence limits of 95% were ≤ 114 ms for the total group, ≤ 120 ms for men and ≤ 104 ms for women. Normalization of QRS duration for height (normal value <66 ms/m) eliminated any difference between men and women. LAS <40 had an upper value of 48 ms in the total group, 46 ms in men and 50 ms in women. It was not possible to define normal values for RMS-40 because of the wide scattering of data. A significant linear correlation existed among all the signal averaged electrocardiographic parameters; that is, a prolonged QRS duration increases the possibility of having both a longer LAS <40 or a lower RMS-40. Adoption of criteria that are either gender-specific or related to the body characteristics is warranted on the basis of this study. Application of QRS duration corrected for height (normal value <66 ms/m) cancels out any statistical difference between men and women, allowing comparison of patients with different body characteristics.

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Ventricular late potentials represent low-amplitude, high-frequency signals that can be recorded in the terminal portion of the QRS complex and ST segment.¹ Their presence in patients with myocardial infarction has been demonstrated to be associated with a propensity to develop ventricular tachycardia.²⁻⁵ The anatomic changes determined by myocardial infarction cause a slow and inhomogeneous activation of the infarcted area, which may be the site where reentry may occur.⁶ The presence of this slow activation can persist beyond the duration of the ventricular depolarization and are recorded as low-amplitude wave forms in the terminal portion of the QRS complex.

Late potentials are present in normal subjects⁷⁻⁹; therefore, before signal-averaged electrocardiographic values are used as cutoff limits to determine the propensity for developing ventricular tachycardia, it is important to establish normal reference values to ascertain the sensitivity and specificity of the method. This study determines the duration of the signal-averaged filtered QRS (QRS duration), the duration of the low-amplitude signals in the terminal portion of the QRS complex $<40 \mu\text{V}$ (LAS <40), and the root-mean-square voltage in the last 40 ms of the filtered QRS (RMS-40) in normal subjects.

METHODS

Study group: Sixty-one healthy subjects were studied (33 men, 28 women). They were medical residents, nurses and physicians. The mean age was 39 ± 13 (mean \pm standard deviation). None had a history of heart or metabolic disease or systemic hypertension. They had a normal physical examination, standard 12-lead electrocardiogram (ECG) and echocardiogram. No one was a professional athlete or had a body weight that exceeded the upper limits of normal values.

Signal-averaged electrocardiogram: A signal-averaged ECG was recorded after the subjects underwent the standard ECG and echocardiogram ≥ 15 minutes after bed rest and 2 hours after eating. All the recordings were obtained with an Arrhythmia Research Technology 1200EPX high-resolution electrocardiograph. Orthogonal standard bipolar X, Y and Z leads were used to analyze a mean of 246 cycles (range 194 to 385) with a noise level $\leq 0.3 \mu\text{V}$. The recorded signals were amplified, averaged and filtered with a Butterworth bi-directional filter (range 40 to 250 Hz). The signals obtained from the 3 leads were then combined to form a "vector magnitude" $V = \sqrt{X^2 + Y^2 + Z^2}$, which is obtained by taking the square root of the sum of the

TABLE I Clinical and Signal-Averaged Electrocardiographic Characteristics in 61 Healthy Subjects

	Total Group	Men	Women	p Value
Number	61	33	28	
Age (years)	39 ± 13	41 ± 14	38 ± 10	NS
Height (cm)	166 ± 9	173 ± 7	159 ± 6	<0.001
Weight (kg)	69 ± 13	78 ± 10	60 ± 8	<0.001
BSA (M ²)	1.78 ± 0.2	1.92 ± 0.15	1.62 ± 0.12	<0.001
Systolic BP (mm Hg)	124 ± 11	125 ± 11	122 ± 11	NS
Diastolic BP (mm Hg)	77 ± 6	78 ± 6	77 ± 6	NS
QRS duration (ms)	95 ± 10	98 ± 11	92 ± 6	0.006
LAS <40 (ms)	32 ± 8	31 ± 8	34 ± 8	NS
RMS-40 (μV)	33 ± 16	36 ± 17	30 ± 13	NS
Noise (μV)	0.24 ± 0.06	0.23 ± 0.06	0.25 ± 0.06	NS
Cycles	245 ± 42	253 ± 41	235 ± 41	NS

Values are presented as mean ± standard deviation.
 BP = blood pressure; BSA = body surface area; LAS <40 = duration of terminal portion of QRS under 40 microvolts of amplitude; NS = not significant; QRS duration = signal-averaged duration of ventricular depolarization; RMS-40 = root mean square voltage in the last 40 milliseconds of the signal-averaged QRS.

squares. Several measurements were taken into consideration: QRS duration, LAS <40 and RMS-40, all determined at 40 Hz high-pass filtering.

Statistical analysis: Results are expressed as mean values ± standard deviation. Comparison of means was made using Student's *t* test for independent samples. Pearson correlation coefficient was used to determine the relation between the variables. Linear regression analysis was made using signal-averaged electrocardiographic results as the dependent variable (Y) and the clinical characteristics as the independent variable (X).

RESULTS

Signal-averaged ECGs were recorded in 61 healthy subjects. The means and standard deviations of each clinical and signal-averaged electrocardiographic characteristic are listed in Table I. There was no difference between men and women with regard to age, and systolic and diastolic blood pressures. Men were significantly taller, heavier and had a larger body surface area than women. A significant difference was found in QRS duration (98 ± 11 vs 92 ± 6 ms, $p = 0.006$) between men and women; no difference, however, existed with regard to LAS <40 and RMS-40. No correlation was found between QRS duration, LAS <40, RMS-40 and age ($r = -8.6$, $r = 4.3$, $r = 4.7$, respectively; relation not significant).

In the total group, a positive linear correlation existed between QRS duration and body surface area, weight and height ($r = 0.47$, $p < 0.0001$; $r = 0.41$, $p < 0.001$; $r = 0.57$, $p < 0.0001$ respectively); no correlation, however, was found between LAS <40, RMS-40

and body characteristics. A positive linear correlation was found between QRS duration and LAS <40 and a negative linear correlation was found between QRS duration and RMS-40 (Figure 1). LAS <40 and RMS-40 were negatively correlated as well (Figure 2).

Table II lists signal-averaged electrocardiographic values when 95% confidence limits are used. The total group showed an upper value of 114 ms for QRS duration; men had a higher upper value (120 ms) than women (104 ms). LAS <40 had an upper value of 48 ms for the total group, whereas the value was 46 ms in men and 50 ms in women. RMS-40 had such a wide range of normal limits that it was not possible to consider these limits as cutoff values.

DISCUSSION

Previous studies have dealt largely with patients with coronary artery disease; few studies have been conducted in healthy subjects.⁷⁻⁹ In a recent report, late potentials were considered abnormal when, at 40-Hz high-pass filtering, the filtered QRS duration was >114 ms, the LAS <40 lasted >38 ms and the RMS-40 was <20 μV.¹⁰ We found the same upper value of QRS duration in healthy subjects, but we obtained a higher value for LAS <40. In the case of RMS-40, it was not possible to extrapolate cutoff values.

Recently, Danford et al⁸ pointed out the difference in filtered QRS duration between men and women. In our study, we found a wide difference of QRS duration between men and women. This is because of different body characteristics; normalization of QRS duration for height in fact eliminates any difference between men and women (Table III). It is not clear why QRS duration is related to body characteristics when the other signal-averaged parameters are not. In 1953 Lipeschkin and Surawicz¹¹ found a relation between the standard 12-lead ECG and body size in healthy subjects: men had a greater QRS duration than women; but when the subjects were grouped by the same height, there was no longer any difference between men and women. They concluded that the difference in QRS duration between men and women was related to differences in height and presumably in heart size. More recently, Levy et al¹²

TABLE II Range of Normal Values Comprised Within 95% Confidence Limits

	Total Group	Men	Women
Number	61	33	28
QRS duration (ms)	76–114	77–120	79–104
LAS <40 (ms)	16–48	15–46	18–50
RMS-40 (μV)	2–64	1–70	4–56

Abbreviations as in Table I.

FIGURE 1. Linear correlation between QRS duration and duration of the low-amplitude signals in the terminal portion of the QRS complex $<40 \mu\text{V}$ (LAS <40) (top) and between QRS duration and root-mean-square voltage in the last 40 ms (RMS-40) (bottom).

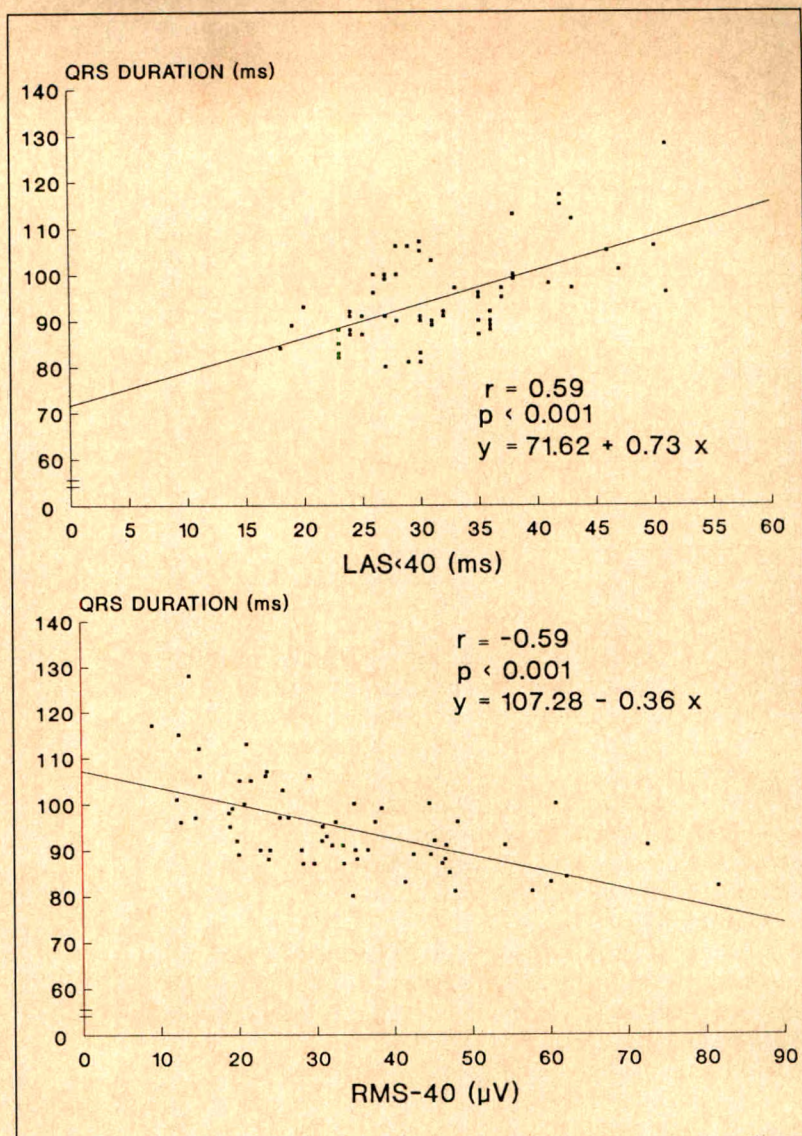


FIGURE 2. Linear correlation between root-mean-square voltage in the last 40 ms (RMS-40) and duration of the low-amplitude signals in the terminal portion of the QRS complex $<40 \mu\text{V}$ (LAS <40).

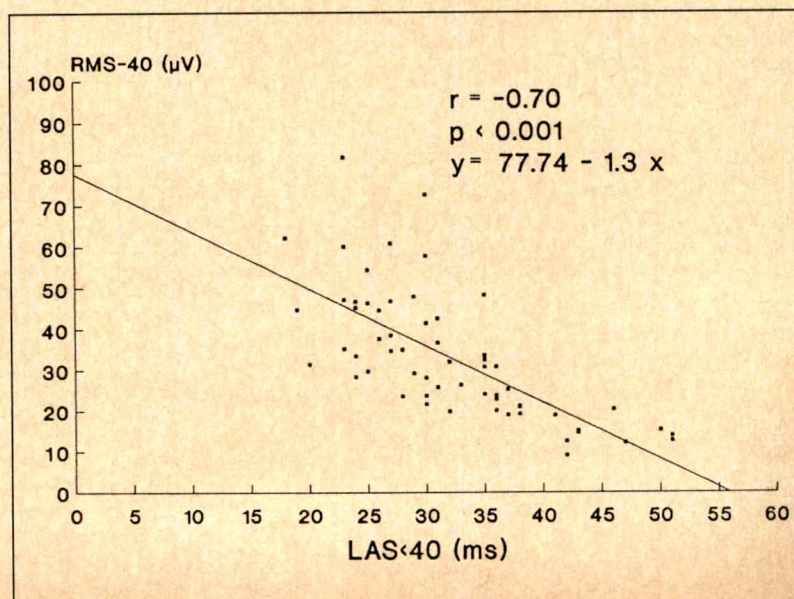


TABLE III QRS Duration Normalized for Body Surface Area, Height and Weight

	Total Group	Men	Women	p Value
QRS/BSA (ms/m ²)	54 ± 8	52 ± 9	57 ± 5	0.01
CL	(39–69)	(34–70)	(47–66)	
QRS/Ht (ms/m)	56 ± 5	56 ± 56	57 ± 3	NS
CL	(47–66)	(45–67)	(50–63)	
QRS/Wt (ms/kg)	1.40 ± 0.25	1.27 ± 0.19	1.55 ± 0.23	<0.0001
CL	(0.9–1.9)	(0.89–1.65)	(1.09–2.01)	

BSA = body surface area; CL = 95% confidence limits range; Ht = height; NS = not significant; QRS = signal-averaged duration of ventricular depolarization; Wt = weight.

TABLE IV Specificity of Previously Reported Values^{9,10}

	Number of False Positives (%)	Specificity
QRS duration (ms)	3 (5)	95%
LAS <40 (ms)	10 (16)	84%
RMS-40 (μV)	10 (16)	84%

Abbreviations as in Table I.

observed an association between left ventricular mass and height. One can therefore speculate, as did Gomes et al,¹ that QRS duration may be the expression of the mass of myocardium that is activated, whereas the other parameters may not be.

Recently, Surawicz¹³ pointed out the moderate sensitivity and low specificity of the test. When we applied the cutoff values detailed in recent reports to our study group, only QRS duration showed an acceptable specificity (Table IV).

The linear correlation among all the signal-averaged parameters in healthy subjects is evidence that these parameters are related to one another (Figures 1 and 2), which means that a prolonged QRS duration increases the likelihood of having both a longer LAS <40 and a lower amplitude of the RMS-40. The linear correlation between QRS duration and body characteristics and among all the signal-averaged parameters leads us to the conclusion that it may be possible to find a wide QRS duration and thus a prolonged LAS <40 and a low RMS-40 in a tall healthy subject.

Our data indicate that the difference in body characteristics between men and women must be taken into account when considering QRS duration. Normalization of QRS duration for height eliminates this difference, allowing comparison of patients with different body characteristics (normal value <66 ms/m). In our study group, LAS <40 had a higher upper normal value than was found in recent reports.^{8–10} No cutoff values could be determined for RMS-40 in our healthy subjects. The application of the previously reported cutoff values to our healthy subjects clarifies the reason for the

low specificity of this test and highlights the fact that only QRS duration seems to have an acceptable specificity.

In our study we dealt only with healthy subjects; patients with organic heart disease with or without sustained ventricular tachycardia were not evaluated. Further studies are needed to evaluate the sensitivity of our values in different clinical settings.

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Validation of a Computerized Technique for Detection of the Gas Exchange Anaerobic Threshold in Cardiac Disease

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Respiratory gas exchange data were collected from 77 men >6 months after acute myocardial infarction. Maximal exercise was performed on an ergometer cycle programmed for a ramp protocol of 15 W/min. The gas exchange anaerobic threshold (ATge) was determined by analysis of the carbon dioxide elimination ($\dot{V}CO_2$) vs oxygen consumption ($\dot{V}O_2$) curve below a respiratory exchange ratio of 1.00 using a computerized algorithm. This value was estimated at the inflection of $\dot{V}CO_2$ from a line with a slope of 1 which intersects the $\dot{V}CO_2$ vs $\dot{V}O_2$ curve. The relation of the ATge to the lactate acidosis threshold was studied in 29 patients. The reproducibility of the ATge method was studied in 77 patients. Mean (\pm standard deviation) $\dot{V}O_2$ for the ATge was 905 ± 220 vs 866 ± 299 ml/min for the lactate acidosis threshold ($r = 0.86$, $p < 0.001$). Mean $\dot{V}O_2$ at the ATge for test 1 was 968 ± 225 vs 952 ± 217 ml/min for test 2 ($r = 0.71$, $p < 0.001$). Mean peak $\dot{V}O_2$ was $1,392 \pm 379$ vs 912 ± 202 ml/min at the ATge ($r = 0.76$, $p < 0.001$). Results demonstrate that this ATge method correlates well with the lactate acidosis threshold, is reproducible, and should be useful as an objective measure of submaximal exercise performance.

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Maximal cardiopulmonary exercise testing is safe, noninvasive, and has been shown to be a valuable tool in the clinical assessment of functional capacity¹ and prognosis.² Although peak results are readily determined, controversy exists regarding the most appropriate methodology for assessment of submaximal exercise performance.³

The highest oxygen uptake ($\dot{V}O_2$) that can be maintained during prolonged exercise without accumulation of lactic acid was termed the anaerobic threshold by Wasserman and McIlroy⁴ in 1964. However, no single method for interpreting gas exchange parameters for detection of the anaerobic threshold has gained wide acceptance. Most methods are subjective and based on manual calculations from plots of ventilatory and gas exchange indexes.⁵

Sue et al⁶ modified the V-slope method described by Beaver et al,⁷ recognizing that the data points of the $\dot{V}CO_2/\dot{V}O_2$ plot above the lactate acidosis threshold had a slope >1 . We created a computer algorithm to simulate this approach, and developed an automated technique for detection of the gas exchange anaerobic threshold (ATge) based on analysis of the carbon dioxide elimination ($\dot{V}CO_2$) vs $\dot{V}O_2$ curve.

On-line, real-time respiratory gas exchange data were collected during maximal exercise in men after myocardial infarction. To evaluate the reproducibility of this technique, we tested patients ($n = 77$) twice within 72 hours. To compare the ATge with the lactate acidosis threshold, a subgroup of patients ($n = 29$) was studied invasively. This report describes the validity of this automated approach for determination of the ATge.

METHODS

Patients: Study A provided lactate data and included 29 men with documented myocardial infarction. The mean age (\pm standard deviation [SD]) was 65.2 ± 9.7 years. Sixteen patients were receiving long-term therapy with β blockers for secondary prophylaxis and 13 patients were receiving long-term therapy with digitalis and diuretics for symptomatic heart failure.

Study B provided data for reproducibility and included 77 men with documented myocardial infarction tested twice within 72 hours. The mean age (\pm SD) was 62.4 ± 7.3 years. Sixty-four patients were receiving β -blocker therapy for secondary prophylaxis and 13 patients were receiving digitalis and diuretic therapy for symptomatic heart failure.

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TABLE I Summary of Results

$\dot{V}O_2$ Mean \pm SD (ml/min)		r	p	n	Mean Difference
Comp. ATge	Manual ATge				
831 \pm 142	803 \pm 147	0.97	<0.0001	33	24 \pm 34
Comp. ATge	LAT				
905 \pm 220	866 \pm 299	0.86	<0.0001	29	39 \pm 158
Comp. ATge	Peak $\dot{V}O_2$				
912 \pm 202	1,392 \pm 379	0.76	<0.0001	77	480 \pm 262
Comp. ATge #1	Comp. ATge #2				
968 \pm 225	952 \pm 217	0.71	<0.0001	77	15 \pm 156
Peak $\dot{V}O_2$ #1	Peak $\dot{V}O_2$ #2				
1,483 \pm 366	1,495 \pm 383	0.94	<0.0001	77	11 \pm 138

ATge = gas exchange anaerobic threshold; Comp. = computer; LAT = lactate acidosis threshold; SD = standard deviation; $\dot{V}O_2$ = oxygen consumption.

All patients had confirmed myocardial infarction >6 months before the study and had completed a rehabilitation program >3 months before the study. No patient had exertional chest pain, and exercise was limited by dyspnea or fatigue. Patients performed routine spirometry to rule out respiratory dysfunction. Informed consent was obtained from the patients and the study protocol was approved by the Norwegian State Drug Regulatory Agency.

Exercise testing protocol: Exercise and gas exchange data were collected continuously using an automated breath-by-breath system manufactured by Medi-

cal Graphics Corporation (System 2001), based on methods previously described by Whipp et al.⁸ Studies were performed using an upright, electrically braked, ergometer cycle (Mijnhardt model KEM III). After a 2-minute rest on the cycle, patients began pedaling at a rate of approximately 65 rpm at a work rate that was programmed to increase smoothly according to a continuous ramp protocol of 15 W/min. Patients were instructed to exercise maximally to exhaustion. A 12-lead electrocardiogram (Kone 620) was interfaced and heart rate recorded continuously. Systolic blood pressure was measured using a manometer cuff against mercury every 3 minutes.

Arterial blood sampling: Arterial blood from the left brachial artery was sampled through an indwelling short polyethylene catheter inserted percutaneously. Sampling commenced at the beginning of the resting stage on the cycle and thereafter every 20 seconds throughout the study.

Lactate assay: Samples were analyzed using a semi-automatic system developed for the transportation of sample aliquots termed "flow injection analysis" based on the controlled dispersion of an injected sample into a continuously moving reagent stream. The method as applied to the assay of lactate has been described in detail by Rydevik et al.⁹ and has been validated against manual enzymatic methods by Karlsson et al.¹⁰

The lactate acidosis threshold is determined by regression analysis of a 2-segment logarithmic plot of serum lactate concentration vs log $\dot{V}O_2$, as described by Beaver et al.¹¹ We have shown that this method correlates well with manually detected lactate acidosis threshold.¹²

Gas exchange anaerobic threshold method: We developed a computerized algorithm to approximate the manual modified V-slope method of ATge detection as

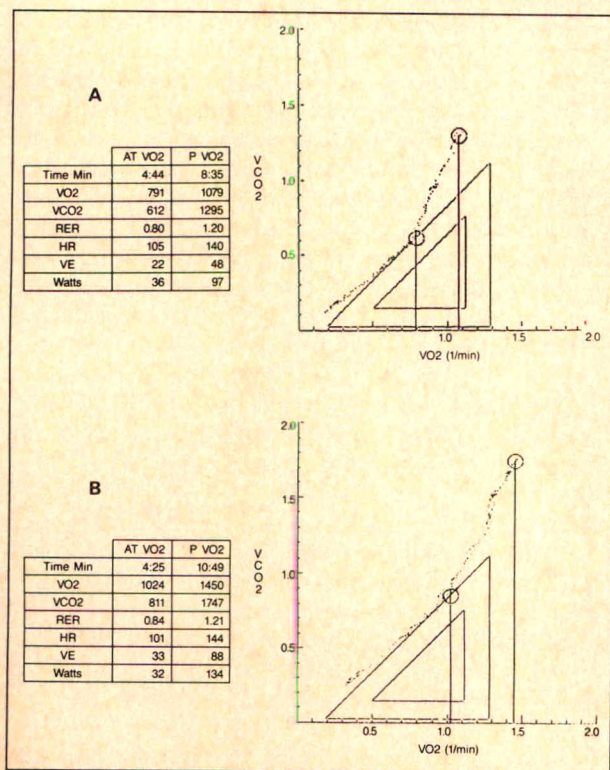


FIGURE 1. Two examples of gas exchange anaerobic threshold (ATge) detection by the computer algorithm. The triangle provides a slope of 1 and facilitates visual inspection. In (A), the peak oxygen consumption ($\dot{V}O_2$) was 1,450 ml/min and the ATge is detected at 1,024 ml/min. In (B), the peak $\dot{V}O_2$ was 1,079 ml/min and the ATge is detected at 791 ml/min. HR = heart rate; RER = respiratory exchange ratio; $\dot{V}CO_2$ = carbon dioxide elimination; VE = ventilation.

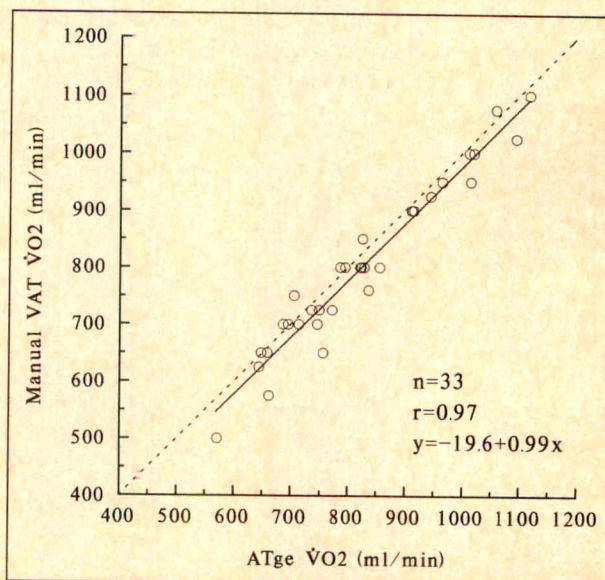


FIGURE 2. A scattergram of computer gas exchange anaerobic threshold (ATge) detection versus manual detection using the technique described by Sue et al.⁶ ($n = 33$). Dotted line is the line of equality; solid line is the line of regression. Mean (\pm standard deviation) differences are listed in Table I. $\dot{V}O_2$ = oxygen consumption.

described by Sue et al.⁶ $\dot{V}CO_2$ is plotted against $\dot{V}O_2$ on equal axes. The anaerobic threshold is located where the rate of rise of $\dot{V}CO_2$ is greater than the rate of rise of $\dot{V}O_2$, coinciding with an increase in the slope of >1.0 . This increase in the slope results from accelerated $\dot{V}CO_2$ and indicates that bicarbonate buffering of lactate is occurring.¹³

The manual method uses a 45° triangle that is brought in from the right parallel to the $\dot{V}CO_2$ vs $\dot{V}O_2$ plot. This facilitates detection of the inflection occurring with a slope >1.0 (Figure 1). The computer program automates this method and analyzes the subset of data with a work load of >5 W and a respiratory exchange ratio of <1.00 . This subset of data was chosen to minimize the obscuring effects of the hyperventilation response at the onset of exercise and the respiratory compensation phase that usually occurs just before termination of peak exercise.

A line with a slope of 1.0 (S1) is drawn through the plot so that 5% of the data points lie below the line. This simulates the manual triangle method and ensures adequate contact with the $\dot{V}CO_2/\dot{V}O_2$ curve. The ATge is detected at the last inflection of the $\dot{V}CO_2$ vs $\dot{V}O_2$ curve from S1.

The basis for using a line with a slope of 1 through the data points before the ATge is based on the empiric observation by many investigators that a regression line drawn through data during this phase of exercise closely approximates a slope of 1.⁶ This is compatible with the use of glycogen as the primary energy source.¹³ S1 is not a linear curve fit and data points falling on this line do not indicate that the respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$) is equal to 1.00, but rather that the ratio of the rate of increase in $\dot{V}CO_2$ vs the rate of increase in $\dot{V}O_2$ approximates 1.

RESULTS

The ability of the program to approximate the manual modified V-slope method for anaerobic threshold detection as described by Sue et al.⁶ was tested. An independent experienced investigator determined the anaerobic threshold using $\dot{V}CO_2/\dot{V}O_2$ plots in a blinded fashion in 33 patients. These results are presented as a scattergram in Figure 2 and in tabular form in Table I. All values are expressed as mean \pm standard deviation. Mean $\dot{V}O_2$ for the manual calculation was 803 ± 147 vs 831 ± 142 ml/min for the computerized ATge ($r = 0.97$, $p < 0.0001$). Mean difference between these 2 methods was 24 ± 34 ml/min. The results of the comparison of ATge with lactate acidosis threshold are displayed in Figure 3 and in Table I. Mean $\dot{V}O_2$ at the ATge was 905 ± 220 compared with 865 ± 299 ml/min for the $\dot{V}O_2$ at the lactate acidosis threshold ($r = 0.86$, $p < 0.0001$). The lactate acidosis threshold ($\dot{V}O_2$ ml/min) was detected significantly earlier than the ATge. Mean difference was 39 ± 158 ml/min ($p < 0.01$).

The correlation between the ATge and the peak $\dot{V}O_2$ is displayed in Figure 4 and listed in Table I. Mean $\dot{V}O_2$ at the ATge was 912 ± 202 compared with $1,392 \pm 379$ ml/min for peak $\dot{V}O_2$ ($r = 0.76$, $p < 0.0001$). Mean difference was 480 ± 262 ml/min.

The reproducibility between 2 consecutive measurements are shown in Figures 5 and 6 and listed in Table I. Mean $\dot{V}O_2$ at the ATge for the first test was 968 ± 225 vs 952 ± 217 ml/min for the second test ($r = 0.71$, $p < 0.0001$). Mean difference between the 2 tests was 15 ± 156 ml/min. Mean peak $\dot{V}O_2$ for the first test was $1,483 \pm 366$ vs $1,495 \pm 383$ ml/min for the second test ($r = 0.94$, $p < 0.0001$). Mean difference between the 2 tests was 11 ± 138 ml/min (difference not significant).

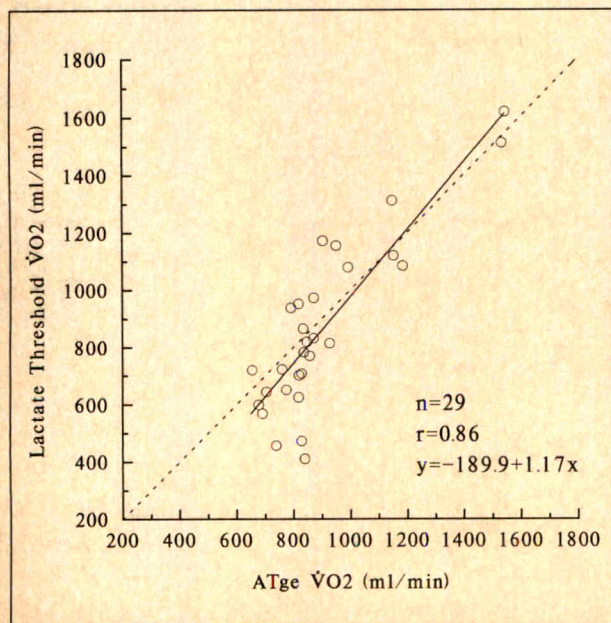


FIGURE 3. A scattergram of computer gas exchange anaerobic threshold (ATge) detection versus lactate threshold ($n = 29$). Dotted line is the line of equality; solid line is the line of regression. Mean (\pm standard deviation) differences are listed in Table I. $\dot{V}O_2$ = oxygen consumption.

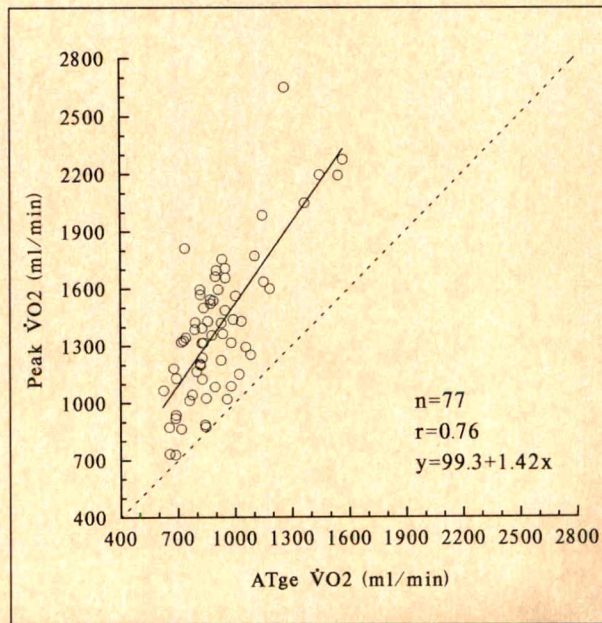


FIGURE 4. A scattergram of computer gas exchange anaerobic threshold (ATge) detection versus peak oxygen consumption ($\dot{V}O_2$) ($n = 77$). Dotted line is the line of equality; solid line is the line of regression. Mean (\pm standard deviation) differences are listed in Table I.

DISCUSSION

The onset of progressive lactate accumulation in the blood reflects glycolysis with increased conversion of pyruvate to lactate. This reaction oxidizes reduced nicotinamide-adenine dinucleotide and permits glycolysis and therefore exercise to continue when the cellular reduced nicotinamide-adenine dinucleotide/nicotinamide-adenine dinucleotide ratio increases. The change in the pattern of gas exchange largely reflects the bicarbonate buffering of lactic acid. Evaluation of the accuracy of gas exchange methods for detecting ATge should therefore be made by comparison with the lactate acidosis threshold.¹⁴ Estimation of the lactate acidosis threshold is based on detection of a systematic increase in lactate concentration during incremental exercise.¹⁵

It has been demonstrated that peak $\dot{V}O_2$ can be determined in patients with coronary artery disease,¹⁶ and we have shown that the results are highly reproducible in such patients.¹⁷ This study demonstrates that the ATge program reliably approximates the manual detection method ($r = 0.97$). The results also indicate that the ATge correlates closely with the onset of a systematic increase in lactate concentration ($r = 0.86$).

The lactate acidosis threshold is detected significantly earlier than the ATge. This bias has a physiologic basis. Beaver et al¹⁸ demonstrated that the bicarbonate decrease is delayed in relation to the lactate increase. This delay may be due to the presence of protein buffers that have a pK similar to the cytoplasmic pH. Subsequently, bicarbonate decreases at an equimolar rate with the lactate increase suggesting that saturation occurs and that bicarbonate is the major buffering mechanism for lactic acid. In the present study, the $\dot{V}O_2$ at the ATge was delayed significantly by 39 ± 158 ml/min compared with the $\dot{V}O_2$ at the lactate acidosis threshold.

The reproducibility of the ATge program was satisfactory ($r = 0.71$) although peak $\dot{V}O_2$ was found to be considerably more reproducible ($r = 0.94$). The consistency of the peak $\dot{V}O_2$ values indicates that the 2 tests were comparable and suggests that maximal exercise is usually required to achieve the reproducibility necessary to detect the effect of intervention. Similarly, although the ATge correlates to peak $\dot{V}O_2$ ($r = 0.76$), the variation is too great to permit accurate estimation of peak exercise performance based on submaximal exercise.

The method described in this report does not condition the gas exchange data although 2 subsets of data are omitted from the analysis. First, because the CO_2 kinetics at the onset of exercise are influenced by rapidly increasing pulmonary blood flow and tissue storage capacity, the data collected during unloaded pedaling and before the 5-W load are excluded from the analysis.

Second, $\dot{V}CO_2$ increases linearly with $\dot{V}O_2$ up to the onset of the anaerobic threshold. At this point the slope of $\dot{V}CO_2$ begins to rise more steeply than the slope of $\dot{V}O_2$. The relation between $\dot{V}CO_2$ and $\dot{V}O_2$ is further characterized by a third phase. Respiratory compensation occurs in response to metabolic acidosis as minute ventilation increases more rapidly than $\dot{V}CO_2$ due to relative hyperventilation. During this final phase, the pattern of $\dot{V}CO_2$ no longer solely reflects metabolic and buffering events in the tissues. Therefore, data collected above a respiratory exchange ratio of 1.00 are not included in the analysis.

This exclusion of the initial and final segment reduces the likelihood of a spurious result by analyzing the slope changes primarily resulting from increased metabolic production of CO_2 . In addition, detection of the ATge by conventional methods is enhanced if the patient exercises to maximal effort. Our program only requires exercise to a respiratory exchange ratio >1.05 .

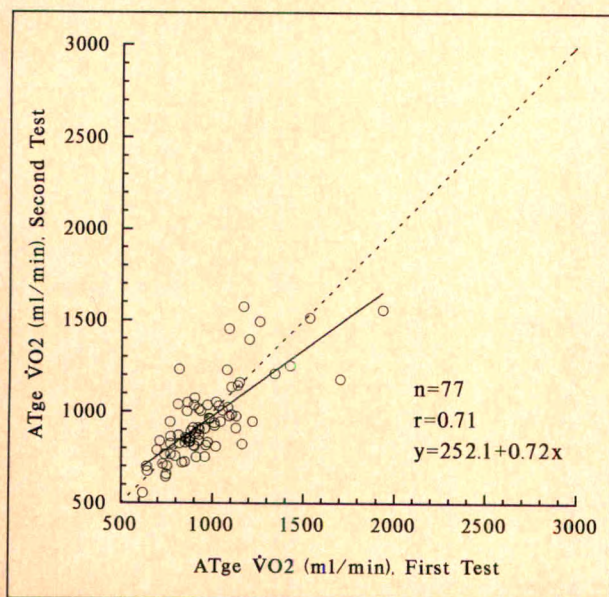


FIGURE 5. A scattergram of computer gas exchange anaerobic threshold (ATge) detection in test 1 vs test 2 ($n = 77$). Dotted line is the line of equality; solid line is the line of regression. Mean (\pm standard deviation) differences are listed in Table I. $\dot{V}O_2$ = oxygen consumption.

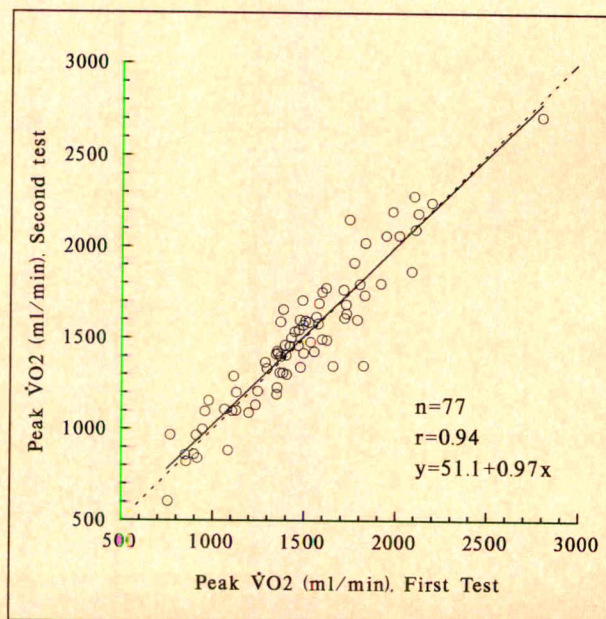


FIGURE 6. A scattergram of peak oxygen consumption ($\dot{V}O_2$) in test 1 vs test 2 ($n = 77$). Dotted line is the line of equality; solid line is the line of regression. Mean (\pm standard deviation) differences are listed in Table I.

Most methods for anaerobic threshold detection are subjective and are based on manual calculations from plots of ventilatory and gas exchange indexes. Such techniques often use identification of the hyperventilation phase from the pattern of minute ventilation, the onset of the nonlinear increase in the respiratory exchange ratio or an increase in the ventilatory equivalent for O_2 without concomitant increase in the ventilatory equivalent for CO_2 .⁶ These methods have shown high test-retest correlation for detection of the anaerobic threshold in experienced laboratories.¹⁹ However, large interobserver variability owing to the subjective nature of manual methods is unavoidable. In addition, such interpretation requires an expertise that limits its general applicability in routine cardiopulmonary exercise testing.

The method detailed in this report compares favorably to the V-slope method described by Beaver et al.¹⁷ The correlation to lactate acidosis threshold ($r = 0.86$) is superior to the previously reported correlation of the V-slope method to lactate acidosis threshold ($r = 0.69$).¹² Correlation to manual detection was also substantially improved ($r = 0.97$ vs $r = 0.83$).¹²

A disadvantage inherent to methods that use regression analysis of the gas exchange data during maximal exercise is the possibility that the hyperventilation phase may be partially included in the calculation. The resultant increase in $\dot{V}CO_2$ is not of metabolic origin and therefore would detract from the precision of ATge detection. Such methods often require manual adjustment of the upper time limit that substantially influences ATge detection.

Techniques using regression analysis are highly sensitive to alterations in the $\dot{V}CO_2/\dot{V}O_2$ slope that may result from the oscillatory breathing pattern often observed in patients with cardiac disease.²⁰ Cyclic fluctuations in minute ventilation complicate manual detection methods based on analysis of the ventilatory equivalents and end tidal values for O_2 and CO_2 .

Protocols with fixed interval load increments or gas exchange data collected from a mixing chamber will not permit adequate resolution of the ATge.²¹ Accurate resolution requires breath-by-breath analysis of data collected during a continuous ramp protocol.

Theoretically, computer analyses might best interpret large volumes of gas exchange data and most correctly detect the anaerobic threshold. However, although computerized programs may make estimation of the anaerobic threshold effortless, the method is not automated because the same experience and expertise required for manual detection is necessary to ensure that the automatic calculation is physiologically sound and has not incorporated artifact. This technique requires a continuous ramp protocol with a target test duration of 8 to 12 minutes. Gas exchange data must be collected on a breath-by-breath basis and the subject should exercise to a respiratory exchange ratio ≥ 1.05 in order to provide adequate data for analysis.

This program is applicable for ATge detection in large clinical studies evaluating functional capacity in patients with heart failure. Such analysis requires objectivity and the application of uniform criteria. The results demonstrate that the method correlates well to lactate acidosis threshold, is reproducible, and should be useful for assessing submaximal exercise performance.

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Hemodynamic Shear Force in Rupture of Coronary Arterial Atherosclerotic Plaques

S. David Gertz, MD, PhD, and William C. Roberts, MD

Angiographic and necropsy studies have suggested a direct pathogenetic relation among rupture of a coronary arterial atherosclerotic plaque, coronary thrombus formation, and acute myocardial infarction (AMI).¹⁻¹¹ However, the local pathophysiologic factor or factors responsible for the initiation of plaque rupture have not been identified. Suggestions have included hemorrhage into a plaque after injury to vasa vasora; mechanical compression associated with coronary spasm; increased intraluminal arterial pressure; and circumferential tensile stress on the "fibrous cap" of the plaque. In this article we summarize the evidence for and against each of these theories and present the case for hemodynamic (rheologic) shear forces as a factor in the pathogenesis of plaque rupture.

Rupture of vasa vasora: Damage to small vascular channels within atherosclerotic plaques has been suggested by a number of investigators to be a source of plaque hemorrhage,¹²⁻¹⁵ but none has shown how this might result in plaque rupture. Extravasation of erythrocytes from injury to intraplaque vascular channels is known to occur in large plaques, but this has been distinguished from hemorrhage associated with plaque rupture by the absence in the former of associated fibrin and platelets.¹⁶ Moreover, Constantinides,¹⁷ in an analysis of serial sections of 17 cases of fatal coronary thrombosis, showed that the associated plaque hemorrhage could always be traced to an entry of blood from the lumen through the same crack in the plaque. Thus, although intraplaque vascular channels are seen often, it is our experience that they are not seen within lipid-rich pultaceous debris, and there is no evidence that such channels are associated with plaque hemorrhage which accompanies rupture of a coronary atherosclerotic plaque.

Plaque compression by coronary vasospasm: Vasoconstriction or spasm has been proposed as a cause of rupture of an atherosclerotic plaque,¹⁸⁻²⁰ but can vasospasm occur in severely narrowed coronary arteries? The dominant histopathologic component of coronary atherosclerotic plaques is fibrous tissue, and, when the luminal narrowing is severe, the underlying media is often severely attenuated.^{21,22} Nevertheless, angiographic

studies, particularly those involving provocative testing with ergonovine maleate, have identified spasm in coronary arteries at, and in close proximity to, sites of severe luminal narrowing.²³⁻²⁷ Recent experimental studies have suggested that sites of atherosclerotic narrowing may be hypercontractile because of possible loss of endothelial-dependent arterial relaxation associated with structural or functional damage to these cells.^{28,29} Joris and Majno³⁰ and Kurgan et al³¹ reported endothelial desquamation after experimental vasospasm induced by periarterial application of L-epinephrine and calcium chloride. Thus, it appears that vasospasm may occur at sites of atherosclerotic stenosis and that vasospasm may be associated with damage to the arterial intima. However, that vasospasm may cause plaque rupture remains an important but still unanswered question.

Sudden increase in intraluminal arterial pressure: Constantinides reported that intravenous injection of various vasopressor amines, in combination with Russell viper venom, induced thrombus formation associated with plaque fissure and hemorrhage in arteries with advanced atherosclerosis.^{32,33} It was hypothesized, therefore, that plaque fissures can be produced in mammalian atherosclerotic arteries by a sudden surge of intraluminal pressure in synergy with endothelial damage.¹⁷ It can be questioned, however, whether this model provides a sufficiently convincing case for increased intraluminal pressure as a factor in the initiation of plaque rupture, and whether an agent such as Russell viper venom, which can cause endothelial damage, might not by itself contribute to plaque rupture.

Increased circumferential tensile stress: Richardson et al³⁴ recently suggested that the eccentric "pools" of extracellular lipid within the atherosclerotic plaque are associated with increased circumferential tensile stress on the thin residuum of fibrous tissue adjacent to the lumen, particularly during ventricular systole, and that variations in the mechanical strength of the plaque cap, such as that which may result from infiltration of foam cells, might further contribute to the likelihood of rupture at such sites. This hypothesis is based on a computerized reconstruction of the distribution of tensile stress within the arterial wall in response to theoretic elevation of intraluminal pressure. Values for tensile strengths of the various components of the atherosclerotic plaque were obtained from previous studies involving micromechanical testing of samples of intima and media obtained from the coronary arteries of human cadavers. Although the applicability of this model to the biophysical forces generated in vivo in the highly pulsatile coronary arterial system may be questioned, this study pro-

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vides valuable information concerning the potential for components of the atherosclerotic plaque to yield in response to increased lateral pressure forces, which are well within the realm of physiologic possibility.

In the following discussion we present evidence supporting hemodynamic shear forces as a major factor in the initiation of plaque rupture.

Plaque rupture involves plaques heavily laden with extracellular lipid material (pultaceous debris) covered by a thin residuum of fibrous tissue (cap) adjacent to the lumen.^{16,34-36} Morphometric analysis (performed by a computerized technique described elsewhere²²) of Movat-stained sections of the infarct-related coronary arteries of patients who died after their first acute myocardial infarction showed the atherosclerotic plaques at sites of plaque rupture to consist of about 32% pultaceous debris, whereas plaques not associated with rupture contained approximately 5% pultaceous debris (Table I).

Although plaque rupture occurs at sites of luminal narrowing, the degree of narrowing is usually insufficient to reduce the rate of distal coronary blood flow. Histologic study of Movat-stained sections from 101 five-mm-long segments at sites of plaque rupture in the infarct-related arteries of 37 patients with first and fatal acute myocardial infarction showed the lumen to be narrowed by 51 to 75% in cross-sectional area by plaque in 27 (27%) segments; by 76 to 95% in 66 (65%) segments; and by 96 to 100% in 5 (5%) segments³⁷ (Figure 1). By planimetry, with the internal elastic lamina as the perimeter of the luminal circle, the mean percent reduction in luminal cross-sectional area by atherosclerotic plaque alone (of all 5-mm coronary segments) at sites of plaque rupture was $81 \pm 9\%$. Although the latter is significantly greater than the mean percent cross-sectional narrowing of all segments of the infarct-relat-

TABLE I Planimetric Measurements of Components of Atherosclerotic Plaque for All Segments (5-mm Intervals) of the Infarct-Related Coronary Arteries of 17 Patients with Plaque Rupture

Segments with Plaque Rupture (no. of S)	Plaque Components (%)					
	Fibrous Tissue		Calcific Deposits		Pultaceous Debris	
	All S	S >75%	All S	S >75%	All S	S >75%
+	63 ± 14*	63 ± 12	6 ± 9	5 ± 9	32 ± 14	32 ± 14
0	77 ± 13	69 ± 15	14 ± 13	15 ± 15	5 ± 5	12 ± 10
p Value	0.002	0.10	0.02	0.30	0.0001	0.02

* Each number represents the mean percent (\pm standard deviation) of plaque area occupied by the 3 plaque components listed for all 5-mm coronary segments of each patient (all S) or just segments of each patient that were narrowed >75% in luminal cross-sectional area by plaque (S >75%). p values were calculated by paired 2-tailed t tests, no. of S = number of segments.

ed arteries that did not have plaque rupture ($68 \pm 9\%$, $p = 0.002$), this "severe" degree of cross-sectional narrowing corresponds, if considering a perfect circle, to approximately 56% reduction in transluminal diameter by plaque alone, which is insufficient, by itself, to reduce the rate of distal coronary flow substantially. This observation is supported by the necropsy studies of Falk,⁵ which show that, of 103 sites of plaque rupture, the lumen was narrowed, in cross-sectional area, by <75% in 39 (38%), by 75 to 94% in 69 (67%), and >94% at only 12 (12%) sites of plaque rupture. From quantitative high-resolution angiographic studies, the "critical stenosis," beyond which coronary flow is sufficiently reduced to cause symptoms, has been determined to range between 70 and 80% reduction in luminal diameter, which corresponds to approximately 90 to 95% reduction in cross-sectional area.³⁸ Because angiographic images may underestimate the degree of diameter reduction, in that the most narrowed areas are compared to less narrowed and not necessarily normal areas,³⁹ the degree of actual diameter reduction necessary to result in critical reduction in flow might be even greater (Figure 2). In contrast, techniques of specimen preparation for histopathologic study, such as fixation

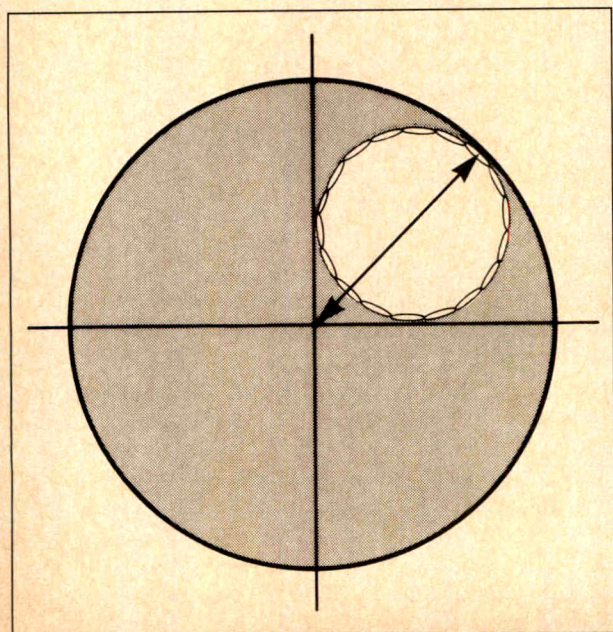


FIGURE 1. Seventy-five percent reduction in cross-sectional area corresponds to approximately 50% diameter reduction.

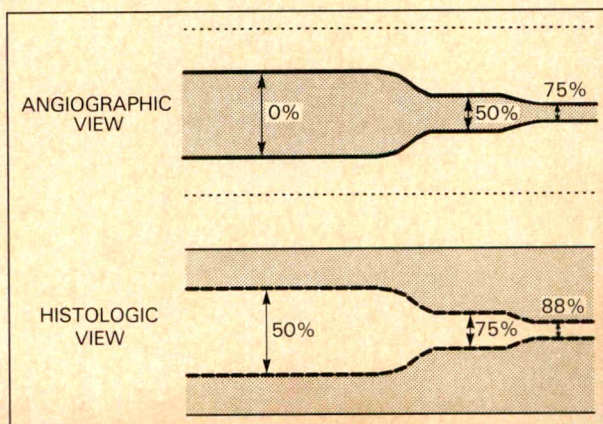


FIGURE 2. Comparison between angiographic and necropsy views of luminal narrowing.

and dehydration, may cause tissue shrinkage and, hence, slight overestimation of absolute values of luminal narrowing.⁴⁰

Angiographic studies have suggested that the degree of stenosis of infarct-related coronary arteries is not a reliable predictor of the time or location of future myocardial infarcts, and that infarcts frequently develop in association with coronary arteries that previously were not severely narrowed.^{41,42} It can be argued that the hypothesis—that coronary arteries subtending a myocardial infarct frequently are not critically narrowed—is not strongly supported by the latter studies, because they were based on angiograms performed weeks to years before the infarction, and these images may underestimate the degree of diameter reduction.³⁹ Nonetheless, we and others have found the lumen at sites of plaque rupture frequently to be narrowed by <75% in cross-sectional area (<50% diameter reduction)—a finding that supports the concept that even moderately narrowed atherosclerotic plaques may rupture.

Hemodynamic wall shear at sites of "subcritical" arterial narrowing has been calculated to be sufficiently strong to cause marked endothelial damage followed by platelet deposition and thrombus formation on exposed subendothelial tissues. Correlative scanning electron microscopic and blood flow studies of the coronary

arteries of dogs and the common carotid artery of rabbits have shown that marked endothelial damage, with extensive platelet deposition and thrombus formation on exposed subendothelial tissues, may occur at the site of a partial arterial constriction (40 to 60% reduction in transluminal diameter) even, and perhaps particularly, when the reduction in luminal diameter is insufficient to alter substantially the rate of distal coronary blood flow.^{30,43} This observation is supported by reports of functional and structural changes in the endothelial lining⁴⁴⁻⁴⁸ associated with arterial curvatures and "flow dividers"⁴⁹ of branch orifices. These sites are normally subjected to increases in the magnitude of wall shear stress (force of the flowing blood, which is parallel to the luminal surface and independent of turbulence) or wide variations in the direction of these forces, or both. This observation is further supported by Fry,⁵⁰ in whose study a partially occlusive, intravascular grooved plug was used to narrow the arterial lumen acutely. He reported that when the shear forces of the blood approach 379 ± 85 dynes/cm², the "acute yield stress of the endothelial surface" in his model system, rapid cellular deterioration occurred, resulting in endothelial desquamation. That shear forces of this magnitude might be possible at sites of plaque rupture in humans can be estimated as follows: By applying Poiseuille's law, shear stress may be expressed as $\tau = 4Q\rho/\pi r^3$, where τ = shear force in dynes/cm², Q = coronary blood flow distal to the site of constriction in ml/s, ρ = viscosity of the blood in units of poise, and r = the luminal radius at the site of constriction in centimeters. Assuming the average luminal diameter of a "normal" coronary artery to be 3.0 mm, the luminal radius of such a coronary artery at the site of a 50% diameter reduction would be 0.075 cm. The average viscosity of the blood, assuming normal hematocrit, is approximately 0.047 poise, and coronary blood flow in, for example, the left anterior descending coronary artery distal to the site of a 50% subcritical stenosis, can be assumed to remain at 150 ml/min with maintenance of normal arterial pressure, although flow may increase more than 3-fold during exercise. The shear force under these conditions is calculated to be 353 dynes/cm², which is well within the range of shear forces hypothesized by Fry to be capable of inducing endothelial damage. These calculations assume steady, laminar flow. Accurate calculations of shear forces in pulsatile arterial systems like the coronary arteries are virtually impossible without knowing the precise velocity profile across the arterial lumen. The marked blunting of the velocity profile that occurs across the arterial lumen in circumstances of pulsatile flow results in a much greater velocity gradient at the arterial wall, especially at sites of arterial constriction, such that it would be reasonable to expect a 5-fold increase or more in shear stress in pulsatile flow over that for the same mean flow rate in steady flow.^{51,52} The shear force might increase even further during exercise, but this increase may be offset at least partially by autoregulatory mechanisms.

It may be argued that just because shear forces cause marked endothelial damage does not prove that

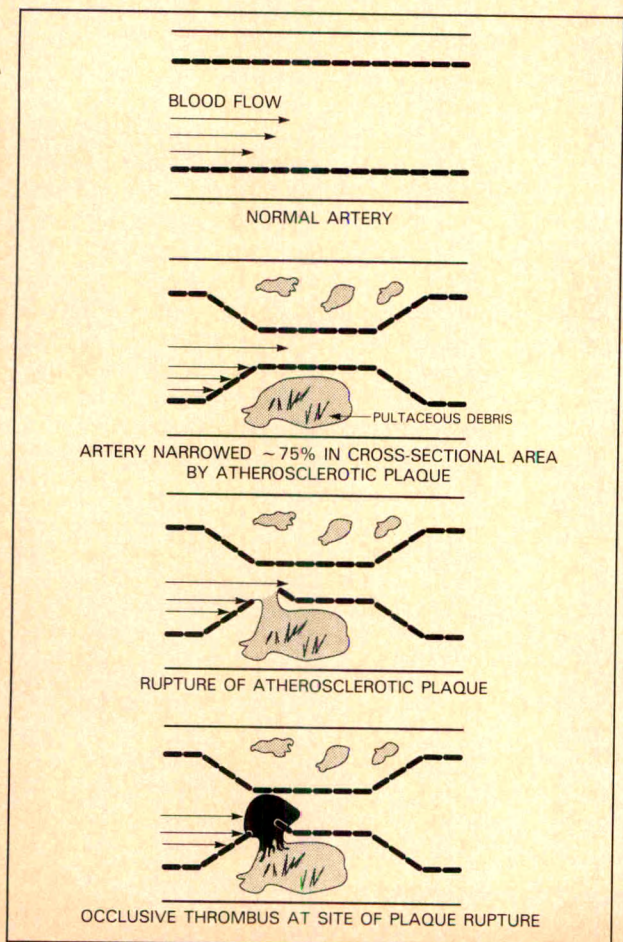


FIGURE 3. Hemodynamic shear force as a factor in rupture of atherosclerotic plaque.

they are capable of causing plaque rupture. Indeed, further multidisciplinary studies are necessary to confirm this hypothesis. Nonetheless, intimal damage thus produced, even if initially of minimal mural depth, may increase the likelihood of rupture at such sites, particularly when occurring in segments with extensive amounts of pultaceous debris and correspondingly thinner residuum of fibrous tissue between the pultaceous debris and the arterial lumen (Figure 3). Exposure of thrombogenic stimuli, such as collagen fibrils and pultaceous debris, followed by platelet adhesion and thrombus formation, may result in partial or total arterial occlusion at such sites by thrombus, with facilitation of such occlusion by superimposed spasm consequent to the release of vasoactive compounds from platelets at the sites of damaged or absent endothelium. Vasoconstriction at sites of endothelial desquamation also might increase the likelihood of plaque rupture, by the mechanical effects of the constriction itself on the arterial wall, or by further increasing the intensity of the hemodynamic shear on the already damaged intima, provided that the constriction remains below the "critical stenosis."

Intimal damage associated with hemodynamic shear might also be expected to facilitate the sequence proposed by Richardson et al,³⁴ by decreasing the circumferential tensile force necessary to rupture the plaque at sites of extensive pultaceous debris and an attenuated fibrous tissue residuum.

Thus, it appears likely that coronary atherosclerotic plaques may rupture even when, and perhaps particularly because, the reduction in luminal cross-sectional area is insufficient to reduce distal coronary flow. Increased shear force associated with the acutely narrowed arterial segments may, by itself, cause intimal damage sufficiently severe to cause plaque rupture, or it may participate with either or both intramural circumferential stress or mechanical forces associated with active vasoconstriction as a component of a multifactorial pathogenesis of plaque rupture.

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Stepped-Down Therapy Versus Intermittent Therapy in Systemic Hypertension

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During the past 30 years many investigators have suggested the possibility of "step-down" therapy and discontinuing therapy in hypertensive patients.¹⁻²⁰ Reducing the dosage of 1 drug or eliminating another in patients after blood pressure has been controlled for a specific length of time is different than discontinuing therapy. Step-down therapy should be reserved for patients with moderately severe or severe hypertension requiring >1 drug to control the arterial pressure, whereas discontinuation of therapy should be considered only in patients with mild hypertension who only need 1 drug. It is obvious, therefore, why the many studies¹⁻²⁰ evaluating discontinuation of therapy have demonstrated such a wide variation of success: 3 to 74%.

In 1978, in an attempt to determine the minimum amount of therapy needed to control arterial pressure in patients receiving multiple antihypertensive agents, I began in a stepwise fashion to reduce the dose of 1 of the drugs and then discontinue use of ≥ 1 of the agents after the blood pressure had been at goal limits for 6 months.²⁰ Of the 51 patients available for the study, 20 were originally receiving 3 antihypertensive agents, and 31 were receiving 2. Each had objective evidence of vascular disease, i.e., fundal changes and electrocardiographic evidence of left ventricular hypertrophy. After 6 months it was possible to eliminate 1 drug or reduce the dose of another in 49 of 51 patients. In addition, there was a significant reduction in the frequency of adverse effects. At the beginning of step-down therapy there were 161 complaints of side effects from the 51 patients. After step-down therapy 29 (18%) reported side effects were unchanged, 42 (26%) were significantly decreased and 90 (56%) were completely absent.

Since these original observations, I have continued with the practice of stepping-down therapy in patients with moderately severe hypertension receiving >1 drug after the diastolic pressure has remained <85 mm Hg for a period of 6 months. Two-hundred forty additional patients have been observed. Therapy has consisted of combinations of a diuretic plus an angiotensin inhibitor plus a β blocker (65 patients), a diuretic plus an angiotensin inhibitor plus a calcium antagonist (72 patients); and a diuretic plus a β blocker (103 patients). In the 137 patients who were originally receiving 3 drugs, we

were able to omit 1 drug in 94 patients (the β blocker or calcium antagonist) and reduce the dose of 1 of the drugs in all the others. In the 103 patients receiving 2 drugs, the diuretic was omitted in 19 and the β blocker was discontinued in 19. Each of these patients has been followed for ≥ 2 years. A 46% reduction in side effects resulted.

Prompted by these observations, the dosage of chlorthalidone (monotherapy) was decreased in a stepwise fashion and then discontinued after the diastolic blood pressure had been maintained <85 mm Hg for 6 months in 67 patients with mild systemic hypertension (diastolic blood pressure 92 to 104 mm Hg).¹ Chlorthalidone therapy was discontinued in 36 of the 67 patients. These patients have now been followed for 7 years.

Since this original study, an additional 135 patients with mild hypertension receiving monotherapy have gone through the step-down routine after their diastolic blood pressure had been <85 mm Hg for 6 months. Therapy consisted of 50 mg of atenolol (61 patients), 10 to 20 mg of enalapril (43 patients) and 240 mg of verapamil (31 patients). Therapy could be entirely discontinued in 65 patients (atenolol in 40, captopril in 12, verapamil in 9). These patients have now been followed for 2 years.

There is no doubt that patients with mild hypertension frequently have a spontaneous reduction to normal levels of diastolic blood pressure after their initial apprehension has been abated. In the Australian trial,²⁰ 48% of patients with mild hypertension treated with placebo over a 3-year period had a reduction in diastolic blood pressure to 95 mm Hg. The short period of pretreatment observation in my studies prevents any assessment of the reason for the decrease in diastolic blood pressure, i.e., a spontaneous decrease or modification of disease by treatment. In my opinion the high-risk nature of these groups precluded a prolonged period of pretreatment observation. The average diastolic blood pressure was 97 ± 6 mm Hg, and there was ophthalmoscopic evidence of arteriovenous nicking in every patient and a strong family history of stroke or myocardial infarction in ≥ 2 members of the immediate family in all but 9 patients. In addition, 84 patients smoked >1 pack a day, 91 were black men, 21 were diabetic and 24 had electrocardiograms with nonspecific T waves.

Nonpharmacologic methods of therapy, particularly cessation of smoking, dietary restriction of sodium or weight loss, might well have produced similar or better therapeutic results. I have usually been unsuccessful in getting patients to stop smoking. The patients in my

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studies were specifically asked not to change their dietary habits so that I could better evaluate the effects of decreasing the dose or discontinuing the drug on diastolic blood pressure. I believe that weight loss and, particularly, reduction of dietary sodium (which I usually have recommended) would most probably increase the number of patients whose therapy could be discontinued. The studies of Langford¹⁴ and Stamler¹⁸ and their co-workers provide further evidence of the positive effects of nutritional therapy as a substitute for drugs in a hypertensive population. I would agree fully with Stamler et al¹⁸ that patients who had stopped drug therapy and concomitantly reduced overweight excess, excess salt intake and alcohol were most likely to remain normotensive after a follow-up of up to 4 years.

I am particularly intrigued with the suggestion of Schmieder et al¹⁷ that a positive cold pressor test in patients with mild hypertension might be helpful in predicting patients who continue to take antihypertensive therapy.

Surely, the fewest drugs administered in lowest dosage needed to control the arterial pressure is a sound pharmacologic principle. The reduction of the number of pills and particularly the times of administration has not only decreased the frequency of side effects and greatly enhanced adherence to therapy, but most important, also has provided the patients with objective evidence of his or her improvement.

Once the arterial pressure has been controlled, particularly if significant adverse effects are present, one should attempt step-down therapy to determine both the minimum number of antihypertensive agents needed and the minimum effective dosage. Eliminating 1 drug or reducing the dose of another has the potential of decreasing side effects, maintaining well-being, enhancing adherence to treatment, and is certainly cost-effective.

In patients with mild hypertension, intermittent rather than life-long therapy may be possible. Thus, in 36 of my 67 original patients (followed for 7 years) and in 65 of my additional 115 patients (followed for 2 years) whose diastolic pressure remained <85 mm Hg after therapy was discontinued, I will not initiate therapy unless the diastolic increases above this level. The addition of a low-sodium diet, weight reduction and a decrease in alcohol consumption will undoubtedly enhance the period of normotension. These patients have

been instructed to have their pressure monitored every 6 months. Elimination of the necessity of daily life-long therapy surely gives the patient with mild hypertension a much brighter outlook.

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A 50-Year-Old Useful Report on Coronary Risk for Noncardiac Surgery

Nanette K. Wenger, MD

Considerable attention is currently devoted to assessing the risk of perioperative coronary events in coronary patients who require noncardiac surgery. Several features have contributed to this heightened concern. First is the high mortality attendant on perioperative acute myocardial infarction, reported at about 60% in many series.^{1,2} Second is the increased prevalence of extensive noncardiac surgical procedures both among patients with known coronary disease and among elderly patients who have a high likelihood of unrecognized coronary disease; perioperative infarction is now the major cause of postoperative death in elderly patients who undergo noncardiac surgery (Figure 1). Third is the delineation, initially in a Cleveland Clinic report³ and subsequently in the Coronary Artery Surgery Study Registry⁴ data that coronary patients after coronary bypass surgery had an operative mortality for noncardiac surgery comparable to that of patients without significant coronary disease. Also pivotal was the determination, again initially based on Cleveland Clinic data, that although 34% of patients evaluated for elective peripheral vascular surgery had severe but "correctable" coronary disease, severe correctable disease was also present in 14% of patients without prior clinical manifestations of coronary disease. Delineation of severe coronary disease among asymptomatic patients scheduled for noncardiac surgery fostered interest in preoperative risk stratification both of patients with known coronary disease and of those at increased risk for its presence.

A multifactorial risk index developed by Goldman et al⁵ highlighted the substantially increased risk status of patients with myocardial infarction within 6 months, age >70 years, evidence of heart failure, hemodynamically significant aortic stenosis, atrial and ventricular arrhythmias preoperatively, poor general medical status, extensive surgery and emergency operation. More recent classifications also emphasize the importance of the clinical profile in the assessment of coronary risk for noncardiac surgery; young patients, women, and patients without angina or myocardial infarction are at low risk for an adverse cardiac outcome and do not require specific risk assessment testing. Older men with

chest pain syndromes and patients with coronary risk factors are considered at moderate risk; older men with known coronary disease and prior signs or symptoms of left ventricular dysfunction are at high risk; and those with unstable coronary syndromes and recent uncompensated heart failure, particularly pulmonary edema, are at very high risk.^{6,7} Patients in the intermediate category require further, generally noninvasive, testing to separate them into high- and low-risk subsets for anesthesia and surgery.

In the application of specialized preoperative cardiac testing, the inability to exercise to an adequate intensity⁸ is considered indicative of a potential high risk. Dipyridamole thallium testing for patients with peripheral vascular disease who often cannot exercise,⁷ more precise evaluation of the dipyridamole thallium imaging by scintigraphic indexes and evidence of reversible left ventricular dilatation,⁹ and preoperative ambulatory electrocardiographic monitoring for silent ischemia¹⁰ are among the suggested test approaches, but none have been studied comparatively. Furthermore, many of these tests were undertaken in patients being evaluated for peripheral vascular surgery; this subgroup has a high concordance of coronary disease with peripheral vascular disease, to the extent that the predictive accuracy of these and other tests for nonvascular surgery cannot be readily extrapolated.

Emphasis remains on the initial clinical recognition of the high-risk subsets who warrant coronary arteriography to delineate severe correctable coronary disease, if correction is feasible given the urgency of the contemplated surgery. Subsequent clinical delineation of an intermediate risk subgroup is needed, for whom noninvasive testing can further clarify risk status.

In this regard, an interesting report of 625 episodes of coronary artery occlusion (acute myocardial infarction), of which nearly 6% were postoperative, merits review. Postoperative infarction was 66% fatal in this series, with 5 patients diagnosed only at necropsy. Two-thirds of patients with postoperative infarction were >60 years; there was a 4.8:1 male to female ratio, despite an equal number of hospital operations by gender. All but 3 patients had a clinical history of coronary disease with moderate to severe symptoms; and coronary sclerosis and narrowing was evident in all patients who came to necropsy. Half of the coronary events occurred within 3 days of surgery, and most operations were classified as major. The investigators cited the difficulty of diagnosis because severe pain was often absent owing to perioperative narcotic and sedative use, and because the myocardial infarction manifestations of shock, dyspnea

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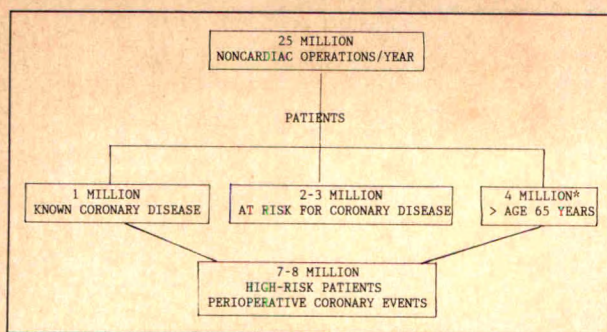


FIGURE 1. Population at risk for perioperative coronary events. *Not included in population known to have or be at risk for coronary artery disease. (Adapted with permission from *Anesthesiology*.¹² Based on data from the National Center for Health Statistics, U.S. Public Health Service, Department of Health and Human Services, 1988; the American College of Surgeons; and the American Society of Anesthesiologists.)

and cyanosis were often difficult to differentiate from those due to surgical shock or pulmonary embolism, or both. They speculated about the mechanism of coronary artery occlusion resulting in myocardial infarction, suggesting either thrombosis on an atherosclerotic plaque or hemorrhage into the plaque. They further postulated that alterations in the coronary circulation might be contributory: (1) shock decreasing venous return, cardiac output, and coronary blood flow; (2) tachycardia decreasing the duration of ventricular diastole and increasing cardiac oxygen demand, causing coronary insufficiency; (3) dehydration decreasing blood volume and increasing blood viscosity; and (4) tissue destruction releasing circulating guanidine, histamine, and so forth, and causing arterial wall damage. Their conclusions emphasized the importance of preoperative cardiovascular evaluation, the need for criteria for operations in elderly patients, and the importance of perioperative attention to blood pressure. The contemporary relevance of this report is remarkable, given its date of publication, April 30, 1938, in the *Journal of the American*

Medical Association.¹¹ It was written by Drs. Arthur Master, Simon Dack and Harry Jaffe, and reviewed postoperative coronary artery occlusion at the Mount Sinai Hospital, New York City, between 1931 and 1937. Precise clinical observation, correlation with available laboratory tests and with the pathoanatomy, defined at necropsy, clearly enabled conclusions comparable to those based on results of high-technology costly test procedures over half a century later. Furthermore, the suggested mechanisms for adverse cardiac output mirror those postulated in 1990.¹²

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Perioperative Myocardial Ischemia and Infarction

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Cardiology in the 1930s: Clinical studies published in the 1930s are rarely referred to in current cardiology journals. I was therefore pleasantly surprised when I received Nanette Wenger's manuscript on "Coronary Risk for Noncardiac Surgery," which appears in this issue of the *Journal*.¹ She summarizes the results of an article on "Postoperative Coronary Occlusion," which I co-authored with Arthur Master and Harry Jaffe and published in 1938.²

It is difficult for the modern young cardiologist to visualize the state of clinical cardiology 50 to 60 years ago. Although primitive compared to the high-technology cardiology practiced today, many important clinical studies were carried out by clinicians, such as Paul D. White, Samuel Levine, Arthur Master, Louis N. Katz, Howard Sprague, and others, which form the basis of current cardiologic practice.

With respect to acute myocardial infarction in the 1930s, clinical diagnosis was based on a complete history, physical findings, chest x-ray and electrocardiogram. The latter consisted initially only of 3 standard limb leads, later supplemented by 1 precordial lead (CF4). Multiple precordial leads became routine in the late 1930s. For confirmation of the diagnosis of acute myocardial infarction, fever, leukocytosis and increased sedimentation rate were helpful, but these were nonspecific findings. None of the specific serum enzyme tests and noninvasive imaging techniques to study ventricular function, wall motion and myocardial perfusion was available, nor were cardiac catheterization and coronary angiography. There also was no available system for continuous monitoring of the electrocardiogram.

To assess ventricular function, we relied on the heart rate, blood pressure and measurements of circulation time (arm-to-tongue and arm-to-lung) and venous pressure performed at the bedside. I learned how to measure cardiac output by the acetylene rebreathing method but it was a laborious and tedious procedure that took at least an hour. Nevertheless, several studies were published on the cardiac output in patients after recovery from acute myocardial infarction.

Despite these handicaps, many important clinical observations on acute myocardial infarction were published. From our own department at Mount Sinai Hospital, these included studies on precipitating and predisposing factors, clinical and diagnostic features, treatment, and prognosis on long-term follow-up. Special

attention was given to cardiogenic shock, congestive heart failure, cardiac arrhythmias and conduction defects. The published studies have been confirmed by more modern techniques.

Postoperative myocardial infarction: Among the aforementioned reports was the one on "Postoperative Coronary Occlusion" discussed by Nanette Wenger.¹ It was based on a review of 625 patients with acute myocardial infarction studied from 1931 to 1937. Wenger found it "remarkable" that our conclusions based on our clinical findings are comparable to those in more current reports based on more modern "high-technology costly test procedures." I agree with her.

The title of our article deserves comment. It reflects the difference of opinion concerning the cause of myocardial infarction, which was prevalent at that time and which continued for many years. Our group believed that acute myocardial infarction was caused by an acute coronary occlusion due to occluding thrombus. There were others who believed that the infarction was primary and the acute thrombosis secondary. We considered that such an infarction caused by coronary occlusion was transmural (now labeled Q-wave infarction). We also believed that infarction could be caused by "acute coronary insufficiency" (now labeled acute ischemia) as a result of a sudden decrease in coronary blood flow or increased myocardial oxygen demand. Such infarction was generally focal or subendocardial (now labeled non-Q-wave infarction). Our title "Acute Coronary Occlusion" reflects our belief that our cases of perioperative or postoperative infarction were caused by acute thrombosis, even though surgery can precipitate many hemodynamic complications that can cause acute coronary insufficiency or acute ischemia without gross infarction. These include hypotension, shock, blood loss, tachycardia, arrhythmias and hypoxia, and may lead to non-Q-wave as well as to Q-wave infarction. It is of interest that all 19 of the 35 postoperative patients in our series who came to autopsy exhibited acute coronary occlusion due to thrombosis.

Mechanism of perioperative coronary thrombus:

Acute thrombosis superimposed on an atherosclerotic plaque is currently attributed to: (1) acute plaque fissuring, dissection or rupture, with platelet deposition and aggregation; and (2) the combination of a severely stenotic lesion, with mild damage on its surface, and a predisposing "thrombogenic stimulus" that may be humoral in nature. In our report,² we mentioned subintimal hemorrhage as a factor; this is now considered a result of intimal fissuring or rupture. We also mentioned humoral as well as hemodynamic factors that could cause acute changes in the vessel wall. Among the former, we mentioned histamine and guanidine. Present

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day humoral factors predisposing to thrombus formation are catecholamines, platelet-derived factors such as serotonin, adenosine diphosphate and thromboxane, and von Willebrand factor, present in plasma, platelets and vessel wall. All these factors are considered important for platelet aggregation and adhesion to the vessel wall.

Conclusion: A panoply of high-technology equipment and procedures are now available to the anesthesiologist and surgeon in modern operating and recovery rooms. It is essential to monitor respirations, oxygen intake, heart rate, and systemic and pulmonary pressures to prevent and detect complications such as intraoperative and postoperative hypoxia, hypotension, shock and hemorrhage, which are the major precipitating factors of acute myocardial ischemia and infarction in patients with coronary artery disease. Because the majority of our cases of infarction were diagnosed in the postoperative period, there may be additional postoperative factors predisposing to coronary thrombosis. These include

changes in fluid balance, catecholamines and thrombotic factors.

Finally, preoperative parameters of ischemia, as discussed by Wenger,¹ may identify the high-risk patient. This suggests that the cause of thrombotic occlusion is probably a severely stenotic plaque with superficial endothelial damage, plus the addition of the previously mentioned thrombogenic stimuli. It is also of interest that anesthesiologists are now monitoring the esophageal echocardiogram in high-risk patients undergoing noncardiac surgery. This sensitive method for detecting myocardial ischemia during surgery may help in preventing perioperative myocardial infarction.

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Ages at Death and Sex Distribution in Age Decade in Fatal Coronary Artery Disease

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A prominent article in the lay press in 1989 stressed that coronary artery disease was an "old person's disease."¹ Apparently many physicians also consider coronary artery disease to be an "old person's disease." Recently, Roberts et al² reported a large series of necropsy patients with fatal coronary artery disease. Using data from the earlier study, these investigators examined the age of death in men and in women with fatal coronary artery disease, the ages at death in the various types of fatal coronary events, and the ages at death in 3 different decades.

This study analyzes 867 patients >30 years of age with fatal coronary artery disease, and each patient was studied at necropsy. None at any time had a coronary bypass operation or another type of cardiac operation, and none ever had coronary angioplasty or another type of therapeutic invasive coronary procedure. The hearts in all patients were examined by WCR and classified by him into 4 modes of death: acute myocardial infarction, sudden out-of-hospital death, chronic congestive heart failure after healing of acute myocardial infarction, and sudden in-hospital death with unstable angina pectoris. Further details on the patients included and the definitions used can be obtained from the earlier study.²

The results are displayed in Figures 1 through 4. The mean age of the 667 men was 60 years, and that of the 200 women, 68 years. Three hundred ninety-three (45%) of the 867 patients died from age 31 to 60 years (343

[87%] were men and 50 [13%] were women) (Figure 1). The percentage of women progressively increased in the 3 decades aged 61 to 70, 71 to 80 and 81 to 90 years. Of the 256 patients aged 61 to 70 years, 53 (21%) were women and 203 (79%) were men; of the 161 patients aged 71 to 80 years, 65 (40%) were women and 96 (60%) were men; and of the 51 patients aged 81 to 90 years, 28 (55%) were women and 23 (45%) were men. Of the entire group of 867 patients, 667 (77%) were men and 200 (23%) were women.

The mean ages of death in the men and women in each of the 4 modes of death are displayed in Figure 2. The group with sudden coronary death had a significantly ($p < 0.05$) younger (55 years) mean age than the other 3 groups; the mean age of the acute myocardial infarction group was significantly ($p < 0.05$) older (65 years) than that of the other 3 groups. The groups with chronic congestive heart failure and unstable angina pectoris had similar and intermediate mean ages (62 and 63 years). The sudden coronary death group and the chronic congestive heart failure group had the highest percentage of men (90 and 86%). In both the acute myocardial infarction and unstable angina pectoris groups the percentage of men was less (66 and 73%).

The ages at death in the men (Figure 3) and in the women (Figure 4) in each of 3 decades (1961 to 1990) according to the 4 modes of death are shown in Figures 3 and 4. No significant changes were noted in the 3 decades in either gender within each of the 4 groups.

These data from 867 patients with fatal coronary artery disease studied at necropsy indicate that the mean

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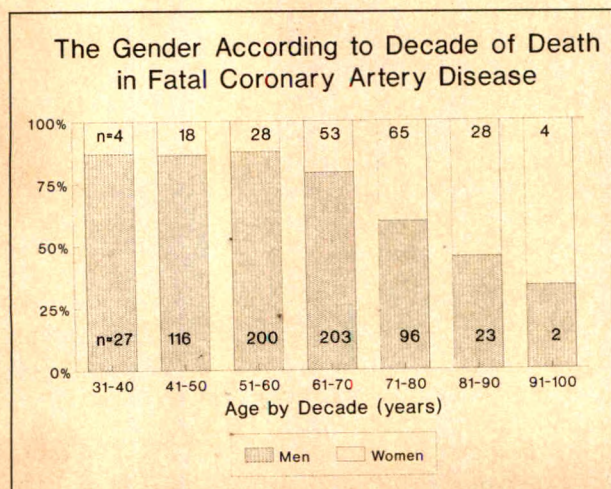


FIGURE 1. Numbers and percent of patients of each sex by age decade with fatal coronary artery disease.

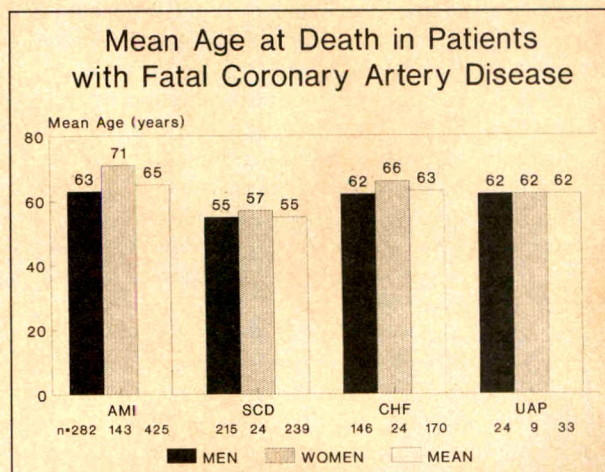


FIGURE 2. Mean age at death in men and women in each of 4 modes of death. AMI = acute myocardial infarction; CHF = chronic congestive heart failure after healing of acute myocardial infarction; SCD = sudden coronary death; UAP = unstable angina pectoris.

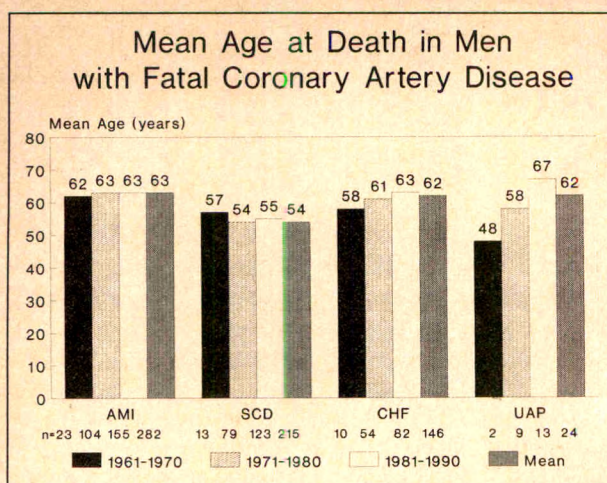


FIGURE 3. Mean age of death in men in the 4 modes of death in each of 3 decades. Abbreviations as in Figure 2.

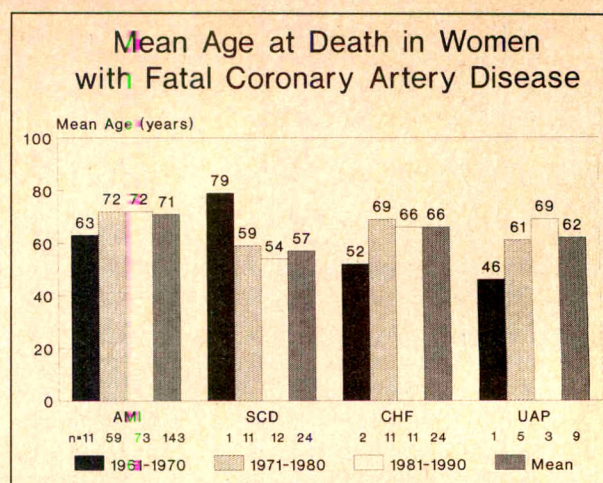


FIGURE 4. Mean age of death in women in the 4 modes of death in each of 3 decades. Abbreviations as in Figure 2.

age of death in the men, who comprised 77% of the patients, was 60 years, and that of the women, who comprised 23% of the patients, was 68 years. The age at death varied a bit depending on the mode of death. The mean age at death was youngest in the sudden coronary death group (55 years), oldest in the acute myocardial infarction group (65 years), and intermediate in the unstable angina pectoris and chronic congestive heart failure groups (62 years).

Although women comprised only 23% of the 867 patients, their percentage increased progressively after age 60 years. Of the 393 patients aged 31 to 60 years, only 50 (13%) were women; in the 61- to 70-year decade, 21% were women; in the 71- to 80-year decade, 40% were women, and in the 81- to 90-year decade, 55% were women. Thus, the gender distribution in any coronary study is in part dependent on the age group of the patients analyzed. A 1939 report by Gordon et al³ on the frequency and extent of atherosclerotic plaques in coronary arteries of 3,400 cases studied at autopsy (data were based on information obtained from autopsy protocols) stated that "... no significant sex difference in the occurrence of coronary changes" was noted after age 70 years.

Some differences in gender also were observed in the various modes of death. Because the mean age of the sudden coronary death group was the youngest of the 4 groups, it might be expected that the frequency of men in this group would be the highest and indeed that was the case (215 of 239 [90%]). Likewise, because the mean age of the acute myocardial infarction group was the oldest, it might be expected that the percentage of men in this group would be the lowest and indeed that was the case (282 of 425 [66%]). In the unstable angina group, 72% were men and in the chronic congestive heart failure group, 86% were men. Thus, the gender distribution in any coronary study is in part dependent on the mode of death or type of coronary event present.

Because none of the 867 patients included had had coronary bypass or angioplasty or any type of cardiac operation or therapeutic invasive procedure, the present data may serve as baseline values for comparison to that

acquired in patients undergoing "revascularization" procedures.

Comparison of the data on age and gender in the present study to that reported earlier by others is difficult for several reasons: (1) The numbers of patients in other studies were insufficient to provide meaningful mean age or gender data; (2) the study was limited to a single gender; (3) the study was limited to a specified age group; (4) the study was limited to a single subset of coronary patients, usually acute myocardial infarction or sudden coronary death; (5) the study did not separate patients with fatal coronary artery disease from those dying from noncoronary causes but in whom coronary atherosclerosis was present at necropsy; and (6) the study did not mention mean age or it was not possible to determine mean age because age was described only in terms of the numbers and percentages of patients in the various age decades. Five reported necropsy studies, all concerning patients with either acute myocardial infarction or sudden coronary death, provided data to which those in the present study can be compared. Bean⁴ in 1938 examined autopsy protocols in 300 patients with fatal acute myocardial infarction: 209 (70%) were men (mean age 60 years) and 91 (30%) were women (mean age 62 years). McCain et al⁵ in 1950 similarly analyzed 281 patients with acute myocardial infarction: 198 (70%) were men (mean age 61) and 83 (30%) were women (mean age 63). McQuay et al⁶ in 1955 similarly analyzed 133 patients with acute myocardial infarction: 81 (61%) were men (mean age 63) and 52 (39%) were women (mean age 68). Silver et al⁷ in 1980 analyzed 100 patients with acute myocardial infarction: 72 (72%) were men (mean age 61) and 28 (28%) were women (mean age 69). Titus et al⁸ in 1973 analyzed 286 patients in whom sudden coronary death was the first manifestation of coronary artery disease: 213 (74%) were men (mean age 58) and 73 (26%) were women (mean age 62).

In summary, the mean age of men with fatal coronary artery disease is about 8 years younger than that of women. The gender distribution in any coronary study is in part dependent on the age group of the patients analyzed,

and in part on the mode of death or type of coronary event present.

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Relation of Angiographic Detected Intracoronary Thrombus and Silent Myocardial Ischemia in Unstable Angina Pectoris

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In patients with unstable angina pectoris, angiographically detected intracoronary thrombus occurs frequently¹ and is associated with a worse prognosis, independent of the extent of disease.² Recently, the presence and duration of silent ischemia have been shown to be powerful predictors of outcome in unstable angina.³ If thrombus is the key mediator of unstable angina, and if silent ischemia is an important measure of disease activity, it is reasonable to suspect a relation between these 2 phenomena. Because the relation between intracoronary thrombus and silent myocardial ischemia has not been previously explored, we studied this in patients with unstable angina whose angiographic and Holter data were previously reported.²⁻⁴

Over a consecutive period of 28 months, beginning in January 1985, 196 patients with unstable angina as previously defined⁷ were enrolled into the study if they were seen within 24 hours of the last rest ischemic chest pain. Heparin and aspirin were not routinely used at the time of the study and the results of Holter monitoring were unavailable to the attending cardiologists. All patients gave informed consent and the protocol was conducted in a manner approved by a University of Toronto ethics review committee.

Twenty-four-hour ST-segment monitoring was begun 6.5 ± 5.9 hours after the qualifying episode of chest pain. We used a 2-channel, on-line computer-based digital Holter system (Medicomp, Epicardia HC) with a frequency response of 0.05 to 100 Hz. An episode of ischemic ST shift from baseline was considered to be present if ≥ 1 mm (1 mm = 0.1 mV) ST elevation or horizontal or downsloping ST depression 80 ms from the J point was present for ≥ 1 minute and separated from other episodes by ≥ 10 minutes.

Selective coronary angiography was performed 4.2 ± 2.6 days after admission. A stenosis of $\geq 50\%$ narrowing

of the lumen was considered significant and was assessed in multiple views by 3 experienced, independent observers who were unaware of the results of Holter monitoring. The definitions for intracoronary thrombus and complex morphology have been previously reported.^{5,6}

Results are represented as mean values \pm standard deviations. Because the distribution of ST shift duration was non-Gaussian, we performed log transformation that resulted in normalization of the data. Continuous variables were compared with unpaired t test and discrete variables with chi-square analysis.

Among the 196 patients recruited, 24 had enzymatic evidence of myocardial infarction and 37 did not undergo Holter monitoring for technical reasons and were excluded. The remaining 135 patients constituted the study group (93 men and 42 women, mean age 57 ± 10 years).

Among the 135 patients, 49 were found to have thrombus, whereas 86 did not. Comparison of clinical characteristics between these patients is shown in Table I: Among those with thrombus, there were more patients who were male, had previous myocardial infarction, and were receiving β blockers.

TABLE I Clinical Characteristics

	No Thrombus (n = 86)	Thrombus (n = 49)
Age (years)	57 ± 11	58 ± 9
Female/Male	38/48	4/45*
Cigarette smoking (%)	29 (34)	18 (37)
Systemic hypertension (%)	34 (39)	16 (33)
Diabetes mellitus (%)	7 (8)	5 (10)
Previous angina (%)	59 (69)	32 (65)
Previous myocardial infarction (%)	22 (26)	31 (63)*
Medications		
Nitrates (%)	45 (52)	34 (69)
Calcium antagonist (%)	48 (56)	32 (65)
Beta blockers (%)	30 (35)	26 (53)†
Digoxin (%)	8 (9)	6 (12)
Acetylsalicylic acid (%)	9 (10)	7 (14)
Number of medications	1.4 ± 1.1	$1.9 \pm 1.0†$

* p < 0.001; † p < 0.005.

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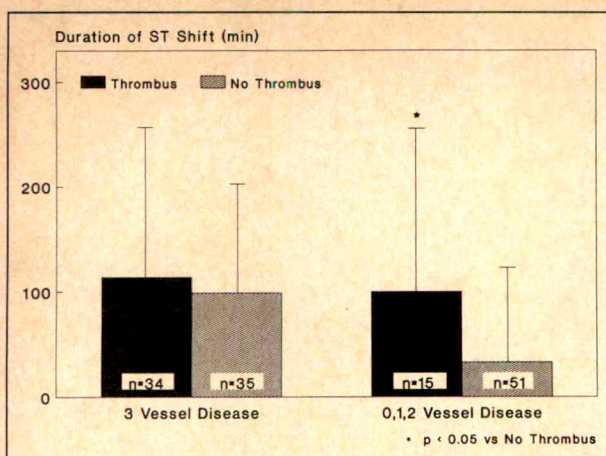


FIGURE 1. Relation of thrombus and extent of coronary artery disease with respect to duration of ST shift.

The incidence of ST shift on Holter monitoring was more frequent in patients with thrombus (80%) than in those without thrombus (58%, $p < 0.025$). Patients with thrombus as compared to those without had a greater duration of ST shift (110 ± 150 vs 60 ± 98 minutes, $p < 0.05$) and a greater number of episodes of ST shift (6.1 ± 6.0 vs 3.5 ± 4.2 , $p < 0.01$). There was no difference between patients with and without thrombus with respect to the magnitude of ST shift (1.8 ± 0.8 vs 1.7 ± 0.8 mm), the frequency of asymptomatic ST shift (93 vs 92%), or the relative frequency of ST elevation (14 vs 13%).

Patients with thrombus had more frequent coronary artery stenoses (2.7 ± 0.6 vs 1.7 ± 1.2 , $p < 0.001$) and a greater prevalence of 3-vessel disease (69 vs 41%, $p < 0.005$) than those without thrombus.

The relation between the severity of coronary artery disease and intracoronary thrombus with respect to ST shift is shown in Figure 1. Among the 69 patients with 3-vessel disease, the duration of ST shift was similar in 34 patients with and 35 patients without thrombus (114 ± 152 vs 99 ± 104 minutes). However, in 66 patients without 3-vessel disease, the 15 with thrombus had a greater ST shift duration (101 ± 152 minutes) than the 51 patients without thrombus (33 ± 85 minutes, $p < 0.05$).

When patients with complex morphology ($n = 81$) rather than those with thrombus alone were compared to those patients without complex morphology ($n = 54$), they also had more frequent ST shift (73 vs 56%, $p < 0.05$), a greater number of episodes of ST shift (5.5 ± 5.7 vs 2.8 ± 3.6 episodes, $p < 0.001$), and a greater duration of ST shift (101 ± 135 vs 44 ± 88 minutes, $p < 0.005$).

Previous studies in patients with unstable angina have shown the prognostic significance of intracoronary

thrombus and silent ischemia.^{3,4} Whereas the association between the extent of coronary artery disease and silent ischemia has been documented,³ the association between intracoronary thrombus and silent ischemia has never been explored.

We found that ST shift, most of which was silent, was more frequent in patients with thrombus. Furthermore, among patients with ST shift, its duration was longer in patients with thrombus. We also found that patients with thrombus had a greater number of significantly diseased vessels, suggesting that, in patients with more severe coronary artery disease, there is a greater opportunity for plaque rupture and thrombus formation.

In patients with 3-vessel disease, the presence of thrombus was not associated with a greater duration of silent ischemia, suggesting that myocardial ischemia may be related to both the severity of coronary artery disease and the presence of thrombus. In patients with 3-vessel disease, the pathophysiology of myocardial ischemia may be related to coronary vasospasm, small platelet emboli, or even small increases in rate pressure product.³

A potential limitation of our study relates to the time interval between ST-segment assessment and coronary angiography, during which intracoronary thrombus could have resolved. However, given the similar frequency and duration of silent ischemia in patients with complex morphology, and the association between complex morphology and thrombus, this limitation is likely unimportant.

In conclusion, intracoronary thrombus in patients with unstable angina is related to both a greater extent of coronary artery disease and to a more frequent presence and duration of silent ischemia. Future studies are needed to explore whether antithrombotic therapy favorably modifies the incidence of silent ischemia and the prognosis of patients with unstable angina.

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Effects of Intracoronary Ergonovine on the Contralateral Coronary Artery in Patients with Atypical Chest Pain

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Ergonovine has become an accepted agent for the provocation of coronary artery spasm. Standard testing protocols generally use either cumulative or single intravenous bolus doses of ergonovine. A disadvantage of such protocols is that spasm may occur in both coronary arteries simultaneously, or during catheter exchange and, if severe, may be difficult to document and manage in some patients with severe myocardial ischemia, especially if using the Judkins technique. Recently, some investigators^{1,2} have begun to administer intracoronary ergonovine to allow selective provocation of spasm in a single coronary artery. It has been postulated that this method might offer more precise control of the vasoconstrictor stimulus and a wider margin of safety than is possible with intravenous administration of ergonovine. In addition, this approach may avoid systemic hypertension and occasional systemic adverse effects that may be seen with intravenous ergonovine. Despite increasing use of intracoronary ergonovine administration in patients, it has not been determined whether such administration causes a truly selective vasoconstrictor effect. The present study determines whether intracoronary ergonovine administration causes selective unilateral coronary artery constriction or whether the contralateral coronary artery is affected as well.

Ten men aged 41 to 70 years, referred for diagnostic cardiac catheterization to evaluate atypical chest pain, were studied. Five patients received ergonovine in the left main artery and 5 in the right coronary artery. All patients were withdrawn from cardiac active medication for ≥ 4 half-lives before the study and no premedication was used. Standard coronary (hand injection) and left ventricular angiography was performed using the Judkins technique (7Fr catheters) and low osmolar contrast medium (Omnipaque) with a 6-inch image intensifier. If all findings were normal during diagnostic left heart catheterization, repeat coronary angiography of either the left main or right coronary artery was performed and filming angles recorded. A catheter exchange was made, followed by a control angiogram of the contralateral coronary artery. After careful verification of catheter tip position, intracoronary ergonovine was administered as a bolus of 10 μg in normal saline given over 30 seconds. Care was taken to avoid spillage of the injectant into the

aorta. Repeat angiography of the vessel into which ergonovine was being administered was performed after 2.5 minutes. Two more doses of ergonovine were then administered in sequence (25 μg each) for a total cumulative dose of 60 μg . Angiography was repeated after each dose and then, after a catheter exchange, a second contralateral coronary angiogram was recorded. The electrocardiogram and aortic pressure were recorded before each angiogram.

Quantitative coronary angiography was performed using a previously validated videodensitometric system that does not require operator edge detection.³ Cross-sectional area was measured for the left main as well as the proximal, mid-, and distal portions of the left anterior descending, circumflex and right coronary arteries. The left main coronary artery was measured just proximal to its bifurcation. The left anterior descending artery was measured proximal to the first septal perforator (proximal segment), just distal to the second septal perforating branch (midsegment) and at a branch point near the apex (distal segment). The circumflex artery was measured just proximal to the origin of the obtuse marginal branch (proximal segment), distal to the obtuse marginal branch (midsegment) and at a distal posterior left ventricular branch (distal segment). The right coronary artery was measured distal to the sinus node artery (proximal segment), distal to the right ventricular branch (midsegment) and distal to the acute marginal branch (distal segment).

Statistical comparisons were made with the 2-tailed *t* test for related measures and significance tested at $p < 0.05$. Results are expressed as mean values \pm standard error of the mean.

No patient in the study had ischemia manifested by angina and ischemic electrocardiographic changes during or after ergonovine administration, although 1 patient did develop transient chest pain without electrocardiographic or angiographic abnormalities. All patients had angiographically normal coronary arteries, left ventriculography (ejection fraction = $62 \pm 2\%$), and hemodynamics.

The effect of intracoronary ergonovine administration into the left main coronary artery is shown in the top half of Figure 1. A dose-dependent vasoconstriction was observed in the proximal, mid-, and distal portions of the left anterior descending and circumflex coronary arteries. Significant constriction of the proximal right coronary artery was observed after administration of ergonovine into the left coronary artery, whereas no significant effect was seen in more distal segment of the vessel. The bottom panel of Figure 1 shows changes seen with intracoronary ergonovine administration into the right coro-

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TABLE I Effects of Intracoronary Ergonovine Administration on Systemic Hemodynamics

Pt. No.	Control				60 µg Ergonovine			
	HR	SAP	DAP	MAP	HR	SAP	DAP	MAP
1	72	125	70	85	72	120	70	86
2	72	160	80	105	90	180	90	120
3	55	120	70	85	60	120	80	93
4	78	120	90	100	62	120	75	89
5	44	140	60	85	40	170	65	100
6	62	120	70	86	71	125	70	88
7	78	140	70	93	75	145	70	90
8	55	90	60	75	55	90	60	75
9	55	90	60	75	55	90	60	75
10	60	120	70	95	60	120	70	95
Mean	63	123	70	88	64	128	71	91
SE	4	7	3	3	4	9	3	4

Patients 1 through 5 had ergonovine administered into the left main artery and patients 6 through 10 into the right coronary artery.
DAP = diastolic aortic pressure; HR = heart rate; MAP = mean aortic pressure; SAP = systolic aortic pressure; SE = standard error of the mean.

nary artery. A similar dose-dependent vasoconstriction was observed in the proximal and midsegments of the right coronary artery, although in 1 patient a distinct increase in the cross-sectional area of the mid- and distal vessel was observed with the initial 10 µg dose (Figure 2). The left main coronary artery also showed a significant vasoconstrictor response after right coronary artery ergonovine administration, although the left anterior descending and circumflex arteries showed no change in either the proximal, mid- or distal segments. Heart rate as well as systolic, diastolic and mean aortic pressures did not change ($p > 0.05$ for all control versus ergonovine comparisons) with ergonovine administration into either the right or left coronary arteries (Table I).

The principle findings of this study are that (1) intra coronary ergonovine causes a dose-dependent vasoconstriction *in vivo*, which may be preceded by vasodilation at lower doses; (2) intracoronary ergonovine does not affect systemic hemodynamics; and (3) vasoconstrictor

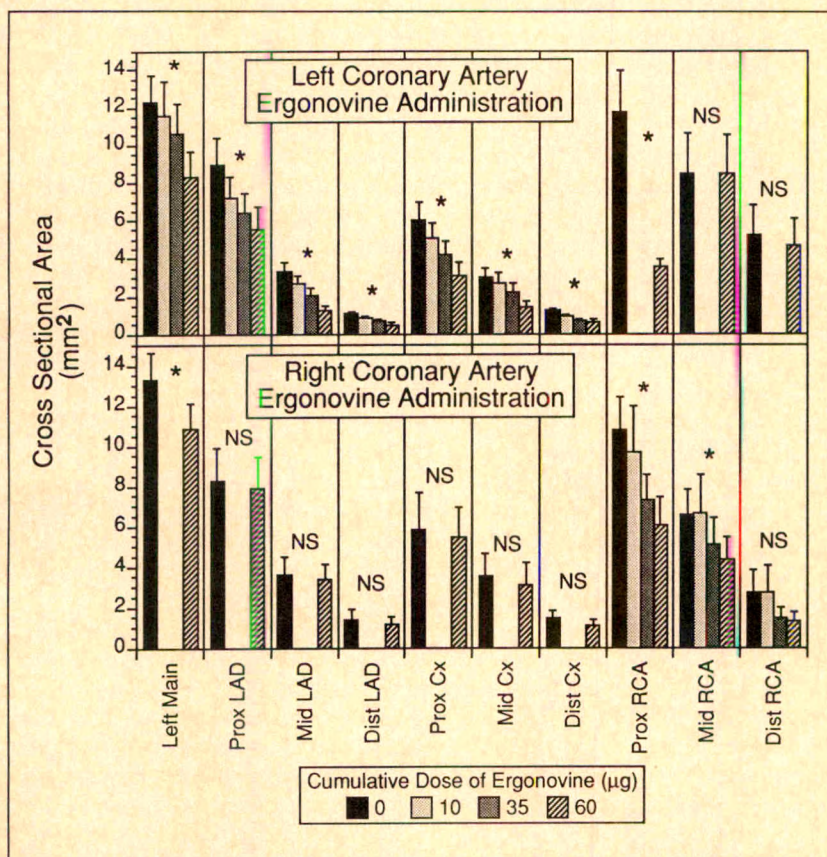


FIGURE 1. Effects of selective administration of ergonovine into the left or right coronary artery (see text). * = $p < 0.05$ for control compared with 60 µg dose; Cx = left circumflex coronary artery; Dist = distal; LAD = left anterior descending coronary artery; Mid = middle; NS = difference not significant; Prox = proximal; RCA = right coronary artery.

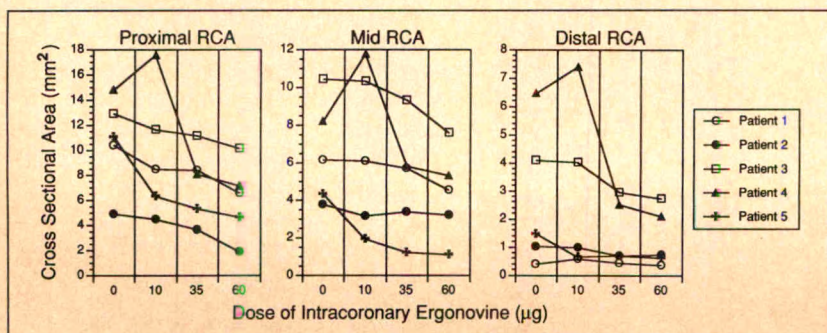


FIGURE 2. Individual patient data for administration of ergonovine into the right coronary artery (see text). Patient 4 showed a distinct vasodilator response with low-dose ergonovine, which was followed by vasoconstriction at higher doses. Abbreviations as in Figure 1.

effects are observed in the proximal portion of the contralateral coronary artery and thus are not selective when administered as in our protocol.

Hackett et al¹ administered intracoronary ergonovine to a maximum cumulative dose of 50 μ g in 6 patients with variant angina and in 9 patients similar to the group included in the current study. In the latter group, intracoronary ergonovine produced vasoconstriction of a similar magnitude as seen in our study; however, proximal, mid- and distal segment responses were not compared and the contralateral coronary artery was not measured. Fournier et al² administered single or repeated intracoronary bolus doses (25 μ g) of ergonovine to 108 patients with normal coronary angiography. Again, ergonovine caused vasoconstriction but no contralateral coronary artery effects were measured.

In general, our data show a dose-dependent ergonovine-mediated vasoconstriction, although in 1 patient all right coronary artery segments revealed vasodilation after 10 μ g (Figure 2), which was overcome with higher doses of ergonovine. Mohri et al⁴ described a similar case, in which a dilator response of both the left and right coronary arteries was observed with 20 μ g intracoronary ergonovine followed by a constrictor response when an additional 35 μ g intracoronary ergonovine was administered. These results are similar to observations of the effect of intravenously administered ergonovine on coronary arterial diameter in dogs. This response has been shown to be biphasic, in the form of an initial dilating action followed by a constricting action.⁵

The magnitude of mean proximal right coronary artery constriction (69%) after administration of 60 μ g ergonovine into the left main coronary artery was greater than the effect seen when ergonovine was administered directly into the right coronary artery (44%). When ergonovine was administered into the right coronary artery, a 19% mean decrease in left main coronary artery area was

observed, whereas a 33% decrease was seen when ergonovine was given directly into the left main. Although these measurements cannot be directly compared because they were obtained from different patients, the magnitude of the responses observed in the proximal contralateral artery is impressive. The mechanism by which intracoronary ergonovine affects the contralateral coronary artery in its most proximal segment cannot be deduced from this observational study. One obvious possibility includes spilling of ergonovine during systole into the contralateral sinus despite precautions taken to prevent this by careful catheter placement and slow injection. Other potential mechanisms include recirculation of ergonovine, preresistance vessel or collateral shunting of blood or local reflexes. In any event, the assumption that one is safely getting a selective unilateral coronary vasoconstrictor effect during intracoronary ergonovine administration is not supported by the data presented herein. Whether this represents a cause for concern clinically must await further studies. Contralateral coronary angiograms should probably always be recorded after intracoronary administration of ergonovine so as not to miss important coronary vasoconstriction that may occur.

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Hypercholesterolemia After Cardiac Transplantation in Children

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Since the 1980s a steadily increasing number of children have undergone cardiac transplantation. Although graft rejection and complications of immunosuppressive therapy are the leading causes of death in children and adults after cardiac transplantation, coronary atherosclerosis is a significant cause of late mortality.^{1,2} Our first pediatric heart transplant patient died suddenly 17 months after transplantation at 3 years of age with severe coronary atherosclerosis. Transplant coronary atherosclerosis may be the result of immune endothelial injury, with a response characterized by proliferation of

myointimal cells, thrombus formation, and ultimate intraarterial deposition of lipid material.³⁻⁵ The development of atherosclerosis in transplanted hearts may be enhanced by the presence of hyperlipidemia, both hypertriglyceridemia and hypercholesterolemia. We measured serial lipid levels in 14 children after heart transplantation to assess the prevalence of lipid abnormalities and the usefulness of niacin therapy in children with significant hypercholesterolemia after transplantation.

The study sample comprised 14 children (aged 6 months to 16 years [mean 8]) who underwent cardiac transplantation. There were 5 girls and 9 boys. Eight of 14 children (57%) received transplants for cardiomyopathy, 1 restrictive, 7 of the dilated type, and 1 caused by anthracyclines. The remaining 6 children had severe ventricular dysfunction with congenital heart disease—4 with complex cyanotic heart disease, 1 with severe aortic

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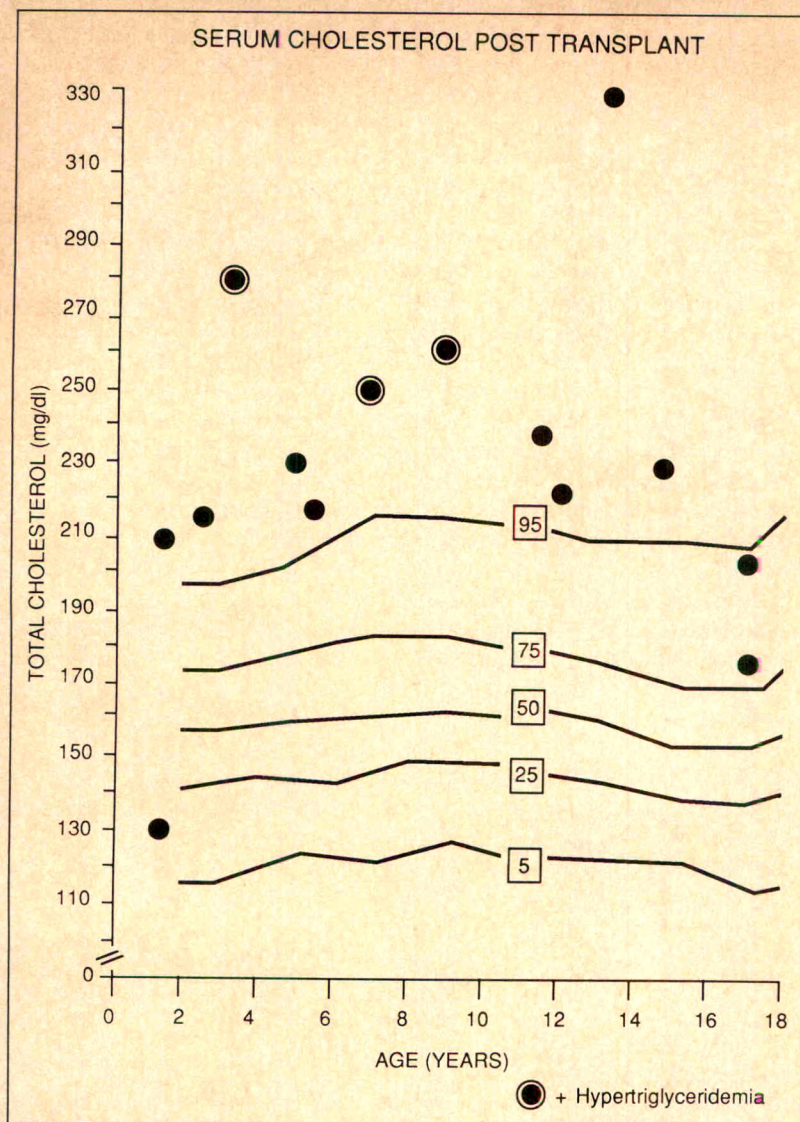


FIGURE 1. Serum total cholesterol in patients (closed bullets) after cardiac transplantation by age as compared to Bogalusa Heart Study⁸ data. Note 3 patients who also have hypertriglyceridemia.

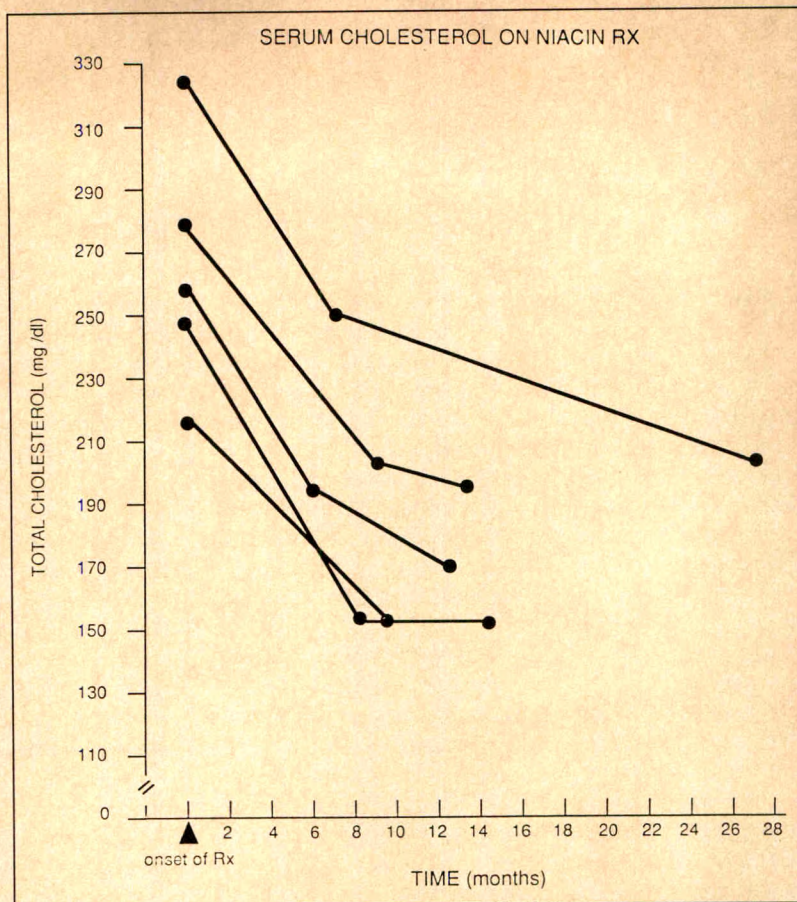
stenosis, and 1 with hypoplastic left heart syndrome. Five patients had undergone previous palliative surgical procedures. The weight for height at the time of assessment after transplantation was greater than the 75th percentile in 6 of 14 patients. All children were maintained on daily prednisone, 0.2 to 0.7 (mean 0.4) mg/kg and on cyclosporine, 5 to 163 (mean 39) mg/kg/day. In addition, azathioprine, 0.5 to 2.4 mg/kg/day (mean 1.4), was used in 10 of 14 patients. All patients had been discharged after transplantation on a low cholesterol diet. Lipid profiles were obtained at 2- to 6-month intervals in association with endomyocardial biopsies. Serum cholesterol and triglyceride concentrations were measured by enzymatic oxidase methods.

Within 2 to 12 months after cardiac transplantation (mean 8.5), 12 of 14 children (86%) had a total serum cholesterol >90th percentile for age by Bogalusa criteria (Figure 1) and >190 mg/dl. Only one child, our youngest at transplantation, had a total cholesterol below the 75th percentile for age. Three of 10 patients also had hypertriglyceridemia. High-density lipoprotein cholesterol ranged from 23 to 65 mg/dl (mean 48).

Whereas previous studies by others have suggested that hyperlipidemia in patients after heart and kidney transplantation is related in some way to the effects of therapy with corticosteroids⁶ and cyclosporine,⁷ no significant correlations were found between serum cholesterol and the daily prednisone dose ($r = -0.16$), daily cyclosporine dose ($r = -0.04$), or the relative body weights of our pediatric patients. The lack of correlation between prednisone dose or cyclosporine dose and serum cholesterol levels in the present study may be due to the small sample size or to insufficient sample variation. While 6 of 14 children in our study had excess weight gain after transplantation, significant hypercholesterolemia was also noted in children who did not gain weight.

Niacin therapy was instituted in 5 patients with cholesterol levels persistently >210 mg/dl, with a mean cholesterol level in these children of 265 mg/dl. Niacin dosage ranged from 50 mg twice a day in the youngest patient (3 years old) to 500 mg twice a day in 2 patients (>9 years). In all 5 children receiving niacin, there was a significant decrease in serum cholesterol ($t = 6.55$; $p < 0.01$), with a mean reduction in serum cholesterol of 73

FIGURE 2. Serum cholesterol change with time after initiation of niacin therapy (RX).



mg/dl (Figure 2). Only 1 child had side effects, mainly flushing, which resolved with the addition of an aspirin with his evening niacin dose. There were no significant changes in cyclosporine levels with niacin therapy.

We conclude that hyperlipidemia, specifically hypercholesterolemia, is a common problem in children >2 years of age after cardiac transplantation. Our results are consistent with previous studies that have shown an increased prevalence of hyperlipidemia in adult transplant recipients.³ Atherosclerosis begins early in life, and the results of the Bogalusa Heart Study demonstrate that the extent of aortic fatty streaks is very strongly related to serum cholesterol levels.⁸ In transplanted hearts, accelerated coronary atherosclerosis has been a documented problem.¹⁻⁵ Most pediatric heart transplant recipients may be at increased risk for development of coronary artery disease, not only because of elevated serum cholesterol levels, but also because of hypertension associated with cyclosporine therapy and with weight gain or obesity after transplantation, which may further increase their cardiovascular risk. Unfortunately, treatment of hyperlipidemia is limited by the availability of effective, well-tolerated drugs that do not adversely affect immunosuppressive therapy, as well as by the limited efficacy of dietary therapy. Niacin therapy seems to be a safe and effective way of treating posttransplant hyperlipidemia in these children.

We recommend periodic monitoring of lipids in children within 2 months of transplantation. Furthermore, in

children over 2 years of age with significant hyperlipidemia (elevated cholesterol, triglycerides, or both), we recommend niacin therapy, beginning with small doses (50 mg) and slowly increasing the dose until the desired effect is achieved, while monitoring for potential side effects. Further research is needed to establish the association of hyperlipidemia after heart transplantation with graft atherosclerosis, and to assess the relation between lipid-lowering therapy and the development of coronary atherosclerosis in patients of all ages after heart transplantation.

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Atrioventricular Nodal Reentry and Dual Atrioventricular Node Physiology in Patients Undergoing Accessory Pathway Ablation

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The finding of dual atrioventricular (AV) nodal pathway physiology, with or without AV nodal reentrant tachycardia, poses a therapeutic dilemma in patients with the Wolff-Parkinson-White syndrome undergoing operative treatment. These findings may be incidental and of no clinical significance or, alternatively, they may indicate the potential for clinical AV nodal reentrant tachycardia. We reviewed the records of 402 patients who had operative therapy for accessory pathways to determine the incidence of dual AV nodal pathway physiology or AV nodal reentry and the clinical significance of these findings.

The records of 402 patients who underwent accessory pathway ablation between May 1981 and October 1989 were reviewed. All patients had preoperative electrophysiologic evaluation, intraoperative mapping and postoperative electrophysiologic testing. Among them, 32 patients (8%) were found to have AV nodal reentrant tachycardia or dual AV nodal pathway physiology; they form the subject of this report. Details of the electrophysiologic study have been described elsewhere.¹ Generally, 3 quadripolar electrode catheters were positioned in the high right atrium, coronary sinus and right ventricular apex, and a tripolar catheter was placed across the tricuspid valve to record the His bundle electrogram. The study included incremental atrial and ventricular pacing and right atrial and ventricular extrastimulus testing at multiple cycle lengths. If tachycardia was not induced or was nonsustained in the baseline state, atropine or isoproterenol, or both, were used.

Intraoperative localization of accessory pathways was obtained by manual sequential mapping of the AV groove during right atrial and ventricular pacing and after induction of reciprocating tachycardia. The postoperative electrophysiologic study was performed at a mean of 6 ± 2 days after the operation using epicardial wires left in situ during the operation. Atrial and ventricular incremental pacing and extrastimulus testing were performed at multiple cycle lengths. Atropine and isoproterenol were generally not used in the postoperative study.

Standard criteria were used to define the locations of the accessory pathways and their participation in reentrant arrhythmias.² "Dual AV nodal pathways" refers to an increase of ≥ 50 ms in AV nodal conduction time after a decrease in atrial coupling intervals of 10 ms,³ or, in the

retrograde direction, to an increase in ventriculoatrial conduction of ≥ 50 ms after a decrease in ventricular coupling interval of 10 ms, in the absence of accessory pathway conduction. Sustained AV nodal reentrant tachycardia and AV node echoes were diagnosed by standard criteria: concentric sequence of retrograde atrial activation, ventriculoatrial interval of < 60 ms at the His bundle recording position, initiation after a critical AH delay and failure to preexcite the atrium by ventricular extrastimulus delivered during tachycardia at a time when the His bundle was refractory.^{4,5} AV nodal reentrant tachycardia was defined as sustained when it persisted for > 30 cycles.

Described surgical techniques were used for interruption of the AV accessory pathway.⁶ After 1985, AV node dissection (skeletonization)⁷ was performed in 6 patients who had pre- or intraoperative inducible sustained AV nodal reentrant tachycardia.

Follow-up was conducted by telephone interviews in December 1989. Follow-up was available in all patients.

Of the 402 patients who underwent surgery for accessory pathway ablation, there were 32 patients with either AV nodal reentrant tachycardia, AV nodal reentry echo beats, or dual AV nodal pathways. There were 21 men and 11 women aged 9 to 67 years (mean \pm standard deviation 28 ± 12). The locations of the accessory pathways were left free wall (24 patients), posteroseptal (5 patients), right free wall (6 patients) and anteroseptal (1 patient). Four patients had 2 accessory pathways. Anterograde preexcitation was present in 20 patients and the remaining 12 patients had a concealed accessory pathway. At a drive pacing cycle length of 600 ms, the mean anterograde effective refractory period of the accessory pathway was 293 ± 57 ms and the mean retrograde effective refractory period was 272 ± 32 ms. Orthodromic AV reciprocating tachycardia was induced in 27 patients, atrial fibrillation in 16 patients and preexcited reciprocating tachycardia in 7 patients. The mechanism of preexcited tachycardia was antidromic tachycardia in 4 patients (using the normal ventriculoatrial conduction system as the retrograde limb); preexcited tachycardia using the first accessory pathway as an anterograde limb and the second accessory pathway as the retrograde limb in 1 patient; AV nodal reentry with bystander accessory pathway conduction in 1 patient; and intraatrial reentry with bystander accessory pathway conduction in 1 patient.

The patients were divided into those with sustained AV nodal reentrant tachycardia (group 1) and those with either nonsustained AV nodal reentrant tachycardia, AV node echo beats or dual AV nodal pathways (group 2). There were a total of 8 patients in group 1. All

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but 1 had the typical form of AV nodal reentry, with a mean tachycardia cycle length of 351 ± 66 ms. One patient had the atypical form of AV nodal reentry (long RP interval). In this patient, conduction over a decremental retrograde accessory pathway was excluded both at surgery and at electrophysiologic study. The diagnosis of AV nodal reentry was made preoperatively in 7 patients and intraoperatively in 1 patient. In 4 patients, the accessory pathway was right-sided, had decremental properties, and did not conduct retrogradely ("pseudo nodoventricular accessory pathway"). Five of the 8 patients in this group had preexcited tachycardia at electrophysiologic study. Operative ablation of AV nodal reentry was performed in 6 patients and was not attempted in the remaining 2 patients, who underwent surgery before 1985.

A total of 24 patients were in group 2. The diagnosis of dual AV node physiology, AV node echo beats or nonsustained AV nodal reentry was made preoperatively in 16 patients, intraoperatively in 2 patients and postoperatively in the remaining 6 patients. Ten patients had dual AV nodal pathways in the anterograde direction, 4 patients had dual AV nodal pathways in the retrograde direction, 6 patients had both dual AV nodal pathways and nonsustained AV nodal reentrant tachycardia, and the remaining 4 patients had nonsustained AV nodal reentrant tachycardia without evidence of dual AV nodal pathways. No patient in this group underwent AV node surgery.

Follow-up ranged from 1 to 101 months (mean of 41 ± 27). In group 1 (those patients with sustained AV nodal reentry) all patients have remained asymptomatic and arrhythmia-free in the absence of any antiarrhythmic drugs. In group 2, a 37-year-old patient died suddenly 4 years after surgery. No symptoms or arrhythmic events were reported during the period between surgery and death. Postmortem examination showed significant coronary artery disease with a previous myocardial infarction. In 1 patient, recurrent sustained paroxysmal supraventricular tachycardia with a short RP interval occurred 5 months after surgery. This patient was subsequently shown to have both atypical and typical forms of AV nodal reentrant tachycardia at electrophysiologic study. Only single atypical AV node echo beats had been demonstrated at the preoperative and postoperative electrophysiologic studies performed at the time of accessory pathway ablation. This patient subsequently underwent AV node skeletonization. The remaining patients have been asymptomatic and arrhythmia-free.

Dual AV nodal pathways with or without AV nodal reentrant echo beats are relatively common electrophysiologic findings, occurring in approximately 10 to 20% of adult patients undergoing electrophysiologic assessment.^{8,9} The frequency of dual AV nodal pathways in patients with accessory pathways is uncertain, because the pattern of AV nodal conduction is frequently obscured by accessory pathway conduction. The frequency of dual AV nodal pathways may have been underestimated

in this study as a result of its retrospective nature and because the postoperative electrophysiologic studies were less extensive than the preoperative evaluation. Nonetheless, the data suggest that concealed dual AV nodal pathway physiology is a relatively common occurrence in patients undergoing surgical ablation of accessory pathways.

The clinical significance of dual AV nodal pathways or AV nodal reentry echo beats in patients with tachycardia due to mechanisms other than AV nodal reentry is uncertain.¹⁰ In this series, 24 patients had either dual AV nodal physiology or nonsustained AV nodal reentry. Twenty-three (96%) have remained free of supraventricular tachycardia after accessory pathway ablation despite these abnormalities. This would suggest that these findings are of minimal clinical significance. One patient with single AV nodal reentry echo beats did develop clinical AV nodal reentrant tachycardia at a later date. Our data would suggest that this is likely to be a rare event. Even the 2 patients who had inducible sustained AV nodal reentry and who did not undergo surgery directed at the AV node have remained asymptomatic. This suggests that this inducible sustained arrhythmia was of minimal clinical significance in these patients.

These results suggest that it should not be necessary to perform concurrent AV nodal reentrant surgery in patients with AV node echo beats or dual AV nodal pathways who are undergoing ablation of an accessory pathway. Subsequent clinical AV nodal reentrant tachycardia was a rare phenomenon in our patients (1 out of 24) and the additional surgical procedure is not without risk. In patients with both sustained AV nodal reentrant tachycardia and accessory pathways, surgical therapy directed at both tachycardia mechanisms can represent a feasible approach with a reasonable success rate.

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Significance of Exercise-Induced Left Hemiblock

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Few published reports^{1,2,4,6,7} have described exercise-induced left hemiblock. It is suggested that this conduction disturbance during exercise is a consequence of decreased blood supply to the conduction bundles and is closely linked to the presence of coronary artery disease. The aim of this retrospective study was to assess the significance of exercise-induced left hemiblock and its relation to a transient myocardial ischemia.

We reviewed the data of 8,684 consecutive patients who underwent exercise stress testing between 1985 and 1989. Twenty-four patients (0.28%) had exercise-induced left hemiblock. Of these, 19 (79%) had been referred for evaluation of typical angina (including 3 after myocardial infarction and 3 after coronary artery bypass surgery), 2 (8%) for atypical chest pain, 3 (12%) for evaluation of arrhythmia and 1 (4%) for evaluation of functional capacity. There were 23 men and 1 woman

aged 34 to 70 years (mean \pm standard deviation 55 ± 10). Three patients (12%) had electrocardiographic evidence of previous myocardial infarction, 2 (8%) had a complete right bundle branch block, 5 (21%) had an incomplete right bundle branch block, 1 (4%) had negative T waves in precordial leads V₁ to V₄ and 14 (58%) had normal electrocardiograms (ECG). In all patients, standing QRS axis at rest was between -30° and 90° .

All patients underwent symptom-limited maximal exercise testing on a treadmill using a standard Bruce exercise protocol. The electrodes were placed below each clavicle and on each iliac crest. Standard 12-lead ECGs were recorded in standing position at rest, during exercise and recovery (on Marquette CASE II[®] from 1985 to 1987, and Case 12[®] from 1987 to 1989). Left hemiblock was defined according to Rosenbaum's⁹ description. Positive criteria for ischemia were a horizontal or downsloping ST-segment depression ≥ 1 mm, measured 0.06 second after the J point, or an ST-segment elevation ≥ 1 mm and $>25\%$ of T-wave amplitude. Thallium-201 stress scintigraphy was performed in 1 patient. Left ventriculography and selective coronary angiography were per-

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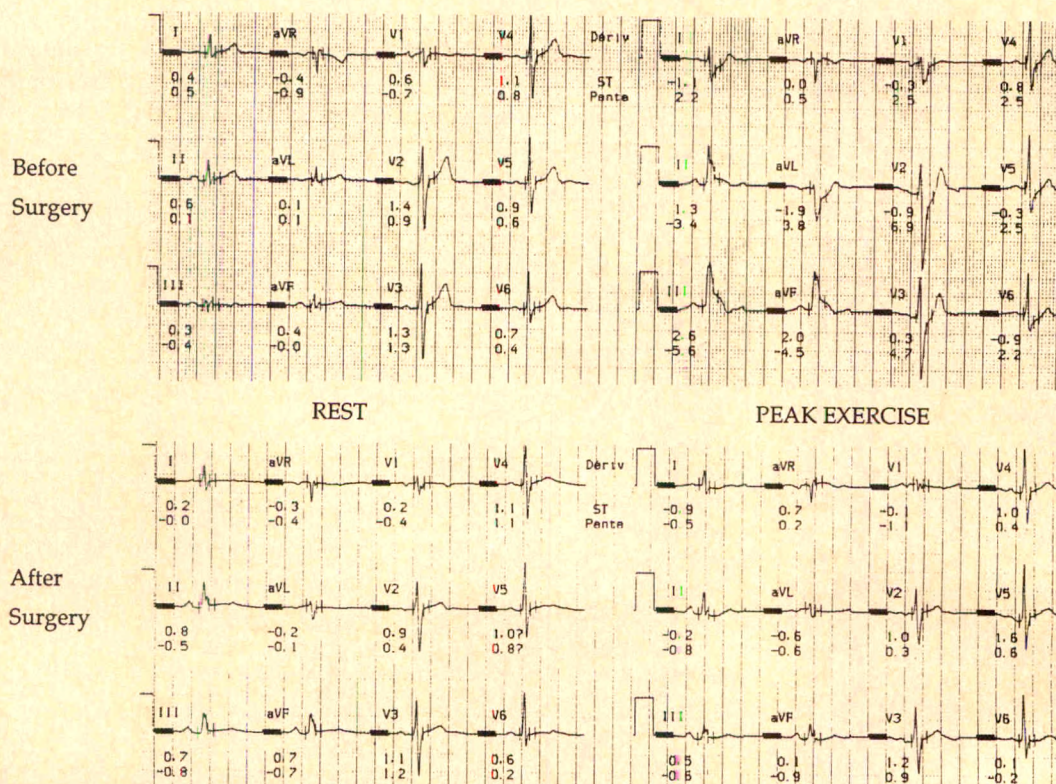
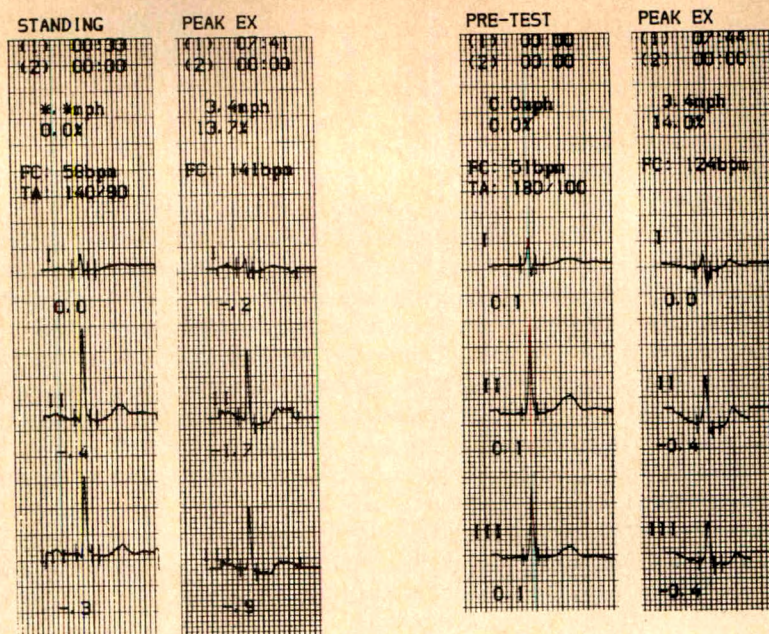


FIGURE 1. Left posterior hemiblock. Patient 16 is a 61-year-old man with recent angina pectoris who underwent exercise testing without treatment. Resting electrocardiogram: incomplete right bundle branch block, QRS axis $+30^\circ$, QRS duration 0.1 second, no ST-T disturbances. At peak exercise: QRS axis $+120^\circ$, QRS duration 0.1 second, ST-segment elevation in leads II, III and aVF. After surgery, incomplete right bundle branch block: QRS axis $+70^\circ$, QRS duration 0.1 second, nonspecific ST-T segment changes at rest and at peak exercise with no QRS axis shift.

FIGURE 2. Left posterior hemiblock with class IC antiarrhythmic treatment. This patient was a 64-year-old man with atypical chest pain who underwent exercise testing with and without flecainide treatment. At peak exercise, without flecainide: QRS axis +90°, QRS duration 0.08 second; with flecainide: QRS axis +120°, QRS duration 0.12 second.



Without treatment

On Flecainide

formed in 20 patients (83%) using the Judkins technique.

The frequency of exercise-induced left hemiblock was low (0.28%). Of the 24 patients with exercise-induced left hemiblock, 11 (46%) had left anterior and 13 (54%) had left posterior hemiblock (Figure 1). Four patients were receiving class IC antiarrhythmic therapy

(3 taking flecainide, 1 propafenone). After withdrawal of the drug, the conduction disturbance disappeared in 2 patients (1 had a normal coronary arteriogram (Figure 2), the other had permeable coronary grafts) and persisted in 1 patient who had coronary graft stenosis (Table I, no. 6). The fourth patient was lost to follow-up. Three patients refused catheterization; nevertheless, all 3 had

TABLE I Exercise-Induced Left Hemiblock—Clinical Data, ECG, Treadmill Test and Angiographic Findings of 18 Patients Free of Class IC Antiarrhythmic Therapy

						Percent Diameter Narrowing of Coronary Artery			
Pt. No.	Age (yr) & Sex	Clinical Data	Resting ECG	QRS Axis	Exercise ST-T	LM	LAD	LC	Right
Left Anterior Hemiblock									
1	60F	AP	T <0 V1V4	60°	ST ↑ V1V2		80		
2	49M	MI-AP	RBBB + MI	20°	ST ↓ V5V6	85			100
3	36M	AP	N	90°	ST ↑ V1V2V3		90		
4	70M	AP	N	20°	ST ↑ V1V2	70	80		
5	56M	AP	N	-30°	ST ↓ V5V6	50	90		
6	64M	CABG-AP	N	0°	ST ↑ V2V3		Graft stenosis		
7*	57M	AP	IRBBB	20°	no change		85		
8*	47M	AP	IRBBB	50°	ST ↑ Q wave V1V4		100		
9	66M	AP	RBBB	10°	ST ↓ V5V6		90	90	90
Left Posterior Hemiblock									
10	53M	MI-AP	MI	60°	ST ↑ III aVF		70	90	100
11	50M	AP	N	90°	ST ↓ V5V6		70	80	80
12	68M	CABG-AP	N	90°	ST ↓ V5V6			90	
13	47M	AP	N	90°	ST ↓ V5V6 ST ↑ V1V2		90		
14	46M	A	N	80°	ST ↓ V5V6				90
15	50M	AP	IRBBB	30°	ST ↑ II III aVF				95
16	61M	AP	N	30°	ST ↑ II III aVF		95		
17	50M	AP	N	30°	ST ↓ V5V6		70	70	100
18	34M	MI-AP	MI	80°	ST ↑ aVL ST ↓ V5V6			80	100

* Previous publication.⁶

A = asymptomatic; AP = angina pectoris; CABG = coronary artery bypass grafting; ECG = electrocardiogram; IRBBB = incomplete right bundle branch block; LAD = left anterior descending; LC = left circumflex; LM = left main; MI = myocardial infarction; N = normal; RBBB = right bundle branch block; Right = right coronary artery.

typical angina pectoris and a positive result on exercise testing. In 1 of these, a thallium-201 stress test showed a lack of uptake in the inferior area, disappearing during redistribution and reflecting a transient myocardial ischemia. This patient was lost to follow-up after the scintigraphy. Eighteen patients underwent coronary angiography: clinical data, exercise testing and angiographic results of these patients are summarized in Table I. Seven patients were receiving treatment at the time of exercise testing but no patient was receiving any drug known to increase QRS duration. Nine patients underwent coronary artery bypass surgery: 1 underwent percutaneous transluminal coronary angioplasty and 8 received medical treatment after the exercise test. Fifteen patients underwent a second exercise test after treatment that showed disappearance of the exercise-induced intraventricular conduction disturbance and ST-T changes in 7 patients (6 coronary artery bypass surgery, 1 percutaneous transluminal coronary angioplasty). In 1 patient, the hemiblock became permanent after coronary bypass surgery with no change in QRS axis during the control test. In the 8 medically treated patients, the exercise-induced left hemiblock was still present in the control test.

Few cases of exercise-induced left hemiblock have been reported. In 1972, Kulbertus and Humblet⁵ reported 4 such cases. In all cases, there was clinical evidence of angina pectoris but coronary artery disease was not documented. The same year, Bobba et al¹ reported 4 cases of exercise-induced left posterior hemiblock. Three patients underwent coronary angiography. In all cases, there was a significant lesion of the right coronary artery, associated in 2 with a left anterior descending stenosis. In 1977, Oliveiros et al⁷ reported 2 cases of exercise-induced left anterior hemiblock with proximal stenosis of the left anterior descending artery. In 1982, Huang and Mathew⁴ described 1 case of exercise-induced left anterior hemiblock associated with proximal left anterior descending artery stenosis. In 1983, Boran et al² reported 4 cases of exercise-induced left anterior hemiblock and 2 cases of exercise-induced left posterior hemiblock with exercise chest pain and ST-segment depression. In all cases, coronary angiography showed a proximal left anterior descending stenosis, associated in 2 cases with right coronary artery stenosis. These conduction disturbances disappeared after medical or surgical treatment.

The development of conduction defects in patients receiving class IC antiarrhythmic drugs has previously been well-described⁸ and relates to mechanisms such as frequency dependence. Thus, in this study, in patients not treated with class IC antiarrhythmic drugs, exercise-induced left hemiblock was associated with coronary artery disease. Clinical results are consistent with this observation: a typical chest pain occurred during exercise testing in 19 of 24 patients. Significant ST changes also appeared in 20 of 24 patients. The unusual frequency of ST elevation in this study (9 of 18) suggests a severe ischemia of

the concerned area (coronary artery narrowings always $\geq 80\%$), confirmed by angiographic findings. The conduction disturbance and the ST-T ischemic changes disappeared after surgical treatment or percutaneous angioplasty in all the documented patients.

Exercise-induced left anterior hemiblock was always associated with significant stenosis of the left coronary artery: the left anterior descending artery at or before the origin of the first septal branch in 7 cases, left main stenosis in 3 cases, and left anterior descending graft stenosis in 1 case. Exercise-induced left posterior hemiblock was associated with severe disease of the right coronary artery in 6 cases, of the left circumflex in 5 cases and of the left anterior descending artery alone in 2 cases. This can be explained by anatomic variations of blood supply to the His bundle.³ In 90% of the cases, blood supply to the anterior hemibranche is dependent on the first septal branch of the left anterior descending artery and blood supply to the posterior hemibranche on the right coronary artery through the atrioventricular nodal artery. In 10% of cases, blood supply to the anterior hemibranche is dependent on the right coronary artery through the atrioventricular nodal artery and blood supply to the posterior hemibranche is dependent on the first septal branch of the left anterior descending.

Exercise-induced left hemiblock is associated with severe coronary artery disease. Left anterior hemiblock suggests, with high probability, a lesion of the left anterior descending (at or before the origin of the first septal branch) or left main artery. Left posterior hemiblock is less discriminatory because the critical stenosis is found mostly on the right coronary or on the left circumflex artery. However, antiarrhythmic treatment with class IC drugs should be considered and a control exercise test after withdrawal of the drug should assess the persistence or disappearance of the conduction disturbance.

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Effects of Encainide and Metabolizer Phenotype on Ventricular Conduction During Exercise

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Genetic factors influence the extent of encainide metabolism. Approximately 93% of the Caucasian population extensively metabolize encainide to O-desmethyl encainide (ODE) and 3-methoxy-O-desmethyl encainide (MODE).¹ In extensive metabolizers, the steady-state plasma concentrations of ODE and MODE are higher than that of encainide during long-term therapy. In poor metabolizers, the metabolic profile is characterized by high concentrations of encainide, low concentrations of ODE, and absent MODE.²

Encainide can produce marked prolongation of intraventricular conduction and this effect is rate-dependent.³ Previous data indicate that ODE and MODE are more potent than encainide in this regard.⁴ Consequently, the electropharmacologic effects of encainide would be expected to differ with respect to the genetically determined capacity to metabolize this drug. Thus, we postulated that extensive metabolizers of encainide would show more marked rate-dependent slowing of intraventricular conduction than would poor metabolizers. The present study determines if rate-dependent intraventricular conduction slowing could be demonstrated in patients receiving encainide during exercise-induced sinus tachycardia, and relates this effect to the genetic phenotype of encainide metabolism.

Nine patients with cardiac arrhythmias who were receiving stable doses of encainide (mean dose 90 mg/day; range 75 to 150) formed the study group. Coronary artery disease with chronic angina was present in 7 pa-

tients, 4 of whom had a history of remote myocardial infarction; 2 patients had no detectable structural cardiac disease; 1 of these 2 had a history of hypertension. Four patients had documented nonsustained ventricular tachycardia, 1 had sustained ventricular tachycardia, and 4 had paroxysmal atrial fibrillation. No patient was receiving concomitant antiarrhythmic therapy. Four age- and disease-matched subjects not receiving encainide served as the control group. Three of these subjects were subsequently placed on encainide therapy, at which time they were included in the study group. All data were collected in the context of routine clinical care. Venous blood samples were collected 5 minutes before exercise testing for analysis of serum concentrations of encainide, ODE and MODE, using a high-performance liquid chromatographic method.⁵ Patients were exercised in the fasting state, 2 hours after the most recent dose of encainide, to fatigue or limiting symptoms on a treadmill, using a Bruce protocol.

Electrocardiographic data were collected digitally using a Marquette CASE-12 Exercise System, with analog outputs of leads I, II, X, Y and Z, connected to a Kiethly-DAS series 500 data-acquisition system. The data acquisition system has a 12-bit resolution for analog-to-digital conversion and was used in conjunction with a Compaq 386 microcomputer. Data were acquired at 1,000 Hz per channel in 9-second collections. Collections were performed twice at rest, once at every 10 beats/min increment in heart rate during exercise and at peak exercise, and once at every 10 beats/min decrement in heart rate during recovery. Data were stored on computer disk for off-line analysis after the exercise test was completed. Acquired data were analyzed by averaging the QRS complexes within each 9-second collection. Af-

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TABLE I Patient Characteristics and Serum Drug Concentrations

Pt. No.	Age (yr) & Sex	Metabolizer Phenotype	Type of Heart Disease	LVEF (%)	Arrhythmia	Chronic Encainide Dosage (mg/8 hours)	Serum Concentration (ng/ml)		
							Encainide	ODE	MODE
1	68M	EM	CAD	37	PAF*	25	4	53	70
2	52M	PM	CAD	34	NSVT	35	598	0	0
3	63M	EM	CAD	75	PAF*	25	375	395	19
4	63M	EM	CAD	57	NSVT*	25	137	254	38
5	67F	EM	SH	65	PAF*	35	112	299	175
6	70M	EM	CAD	55	PAF*	50	130	461	254
7	58M	EM	CAD	55	NSVT*	25	12	235	492
8	30F	PM	NSD	60	SUVT	25	440	100	0
9	62M	EM	CAD	57	NSVT*	25	51	244	40

* Arrhythmia suppression.

CAD = coronary artery disease; EM = extensive metabolizer; LVEF = left ventricular ejection fraction; MODE = 3-methoxy-O-desmethyl encainide; NSD = no structural disease; NSVT = nonsustained ventricular tachycardia; ODE = O-desmethyl encainide; PAF = paroxysmal atrial fibrillation; PM = poor metabolizer; SH = systemic hypertension; SUVT = sustained monomorphic ventricular tachycardia.

ter averaging, the 3 leads that best defined the QRS complex from each of the data collections were displayed and the onset and the offset of the QRS complex was determined, providing the QRS duration. The averaging process reduced root mean square noise by a factor of 3 to 4, depending on heart rate. The resolution of this technique was <2 ms. QRS duration was determined by the consensus of 2 independent observers who were blinded to the genetic phenotype of the patients.

Data are reported as mean values \pm standard deviation. Comparisons between groups were made using

Student's 2 tailed t test. Multilinear regression analysis was used to relate rate-dependent QRS prolongation to serum concentrations of encainide, ODE, MODE and their ratios, and to the percent change in heart rate with exercise. Regression coefficients were determined by analysis of variance. A p value <0.05 was considered statistically significant.

Patient demographics are listed in Table I. All 7 extensive metabolizers demonstrated arrhythmia suppression while receiving encainide as determined by clinical history and electrocardiographic monitoring. One of 2 poor metabolizers, who was treated for nonsustained ventricular tachycardia, failed to demonstrate arrhythmia suppression by serial Holter monitoring. The other poor metabolizer, who was treated with encainide for symptomatic ventricular tachycardia, demonstrated an initial reduction in arrhythmic events on telemetric monitoring; however, subsequent to hospital discharge, the patient again became symptomatic at the end of each encainide dosing interval, and the drug was discontinued because of lack of efficacy.

Extensive metabolizers had mean serum concentrations of ODE plus MODE that were higher in all cases than encainide concentrations during chronic dosing (Table I). The mean daily dose of encainide in the 7 extensive metabolizers was 90 ± 29 mg/day. Similarly, the daily doses of encainide in the 2 poor metabolizers were 75 and 105 mg/day, respectively. Poor metabolizers had high concentrations of encainide and no detectable MODE. One poor metabolizer had no detectable ODE, whereas the other poor metabolizer had a low concentration of ODE relative to encainide.

In all extensive metabolizers of encainide, QRS duration increased progressively during exercise from 117 ± 13 ms at rest to 131 ± 17 ms ($p = 0.002$) at peak exercise, with a mean heart rate increase of 38 beats/min (Figure 1, top; Figure 2, top). The increase in QRS duration varied from 7 to 25% for individual patients, with a mean increase of 12%. In the poor metabolizers, QRS duration was 102 ± 6 ms at rest and 101 ± 6 ms (difference not significant) at peak exercise, with a mean heart rate increase of 65 beats/min (Figure 1, middle; Figure 2, bottom). In the control group, QRS duration was 94 ± 15 ms at rest and 95 ± 15 ms (difference not significant) at peak exercise, with a mean heart rate increase of 58 beats/min (Figure 1, bottom). The mean heart rate increase during exercise for both the poor metabolizers and the control group was significantly greater than it was for extensive metabolizers ($p < 0.005$).

There were no arrhythmias during exercise or in recovery. The correlation between the absolute increase in heart rate during exercise and the degree of QRS prolongation ($r = 0.4$) in individual extensive metabolizer patients was poor. For extensive metabolizers, relative serum concentrations of encainide, its metabolites and their ratios were not predictive of the degree of exercise-induced QRS prolongation (difference not significant).

The QRS duration of the resting electrocardiogram was compared in individual patients before and after treatment with encainide. In 6 of 7 extensive metabo-

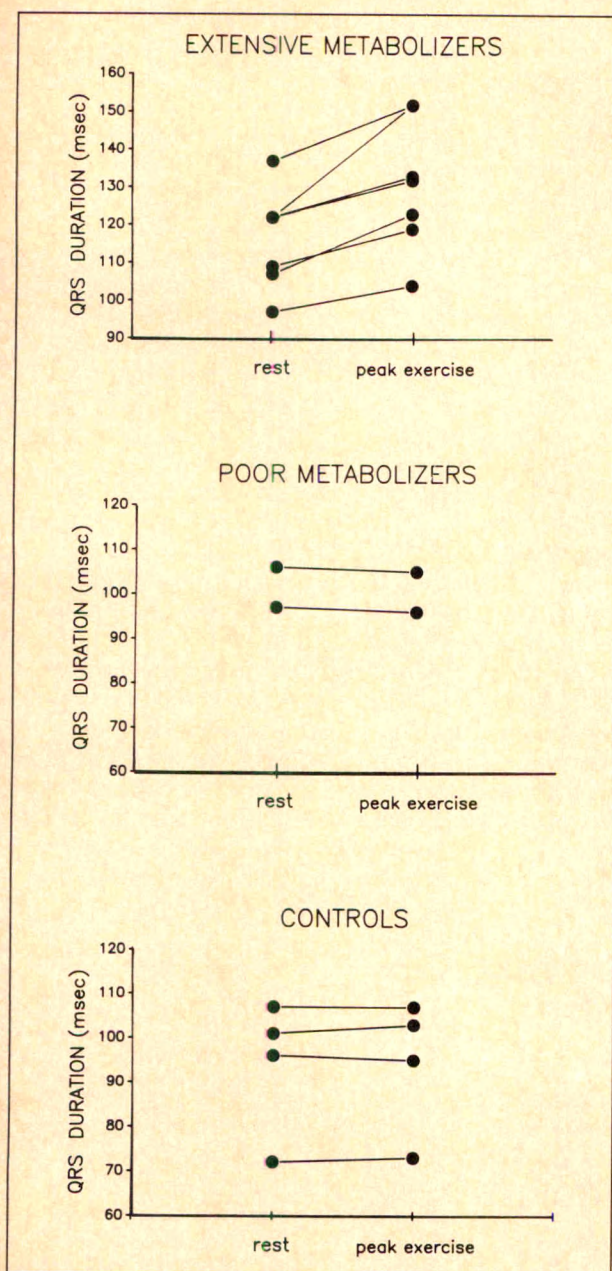


FIGURE 1. The QRS duration at rest and peak exercise in extensive metabolizers of encainide (top), poor metabolizers (middle) and in the control group (bottom). In all extensive metabolizers ($n = 7$), the QRS duration increased progressively during exercise ($p = 0.002$). In the poor metabolizers ($n = 2$), and in the control group ($n = 4$), no changes in the QRS duration occurred from rest to peak exercise.

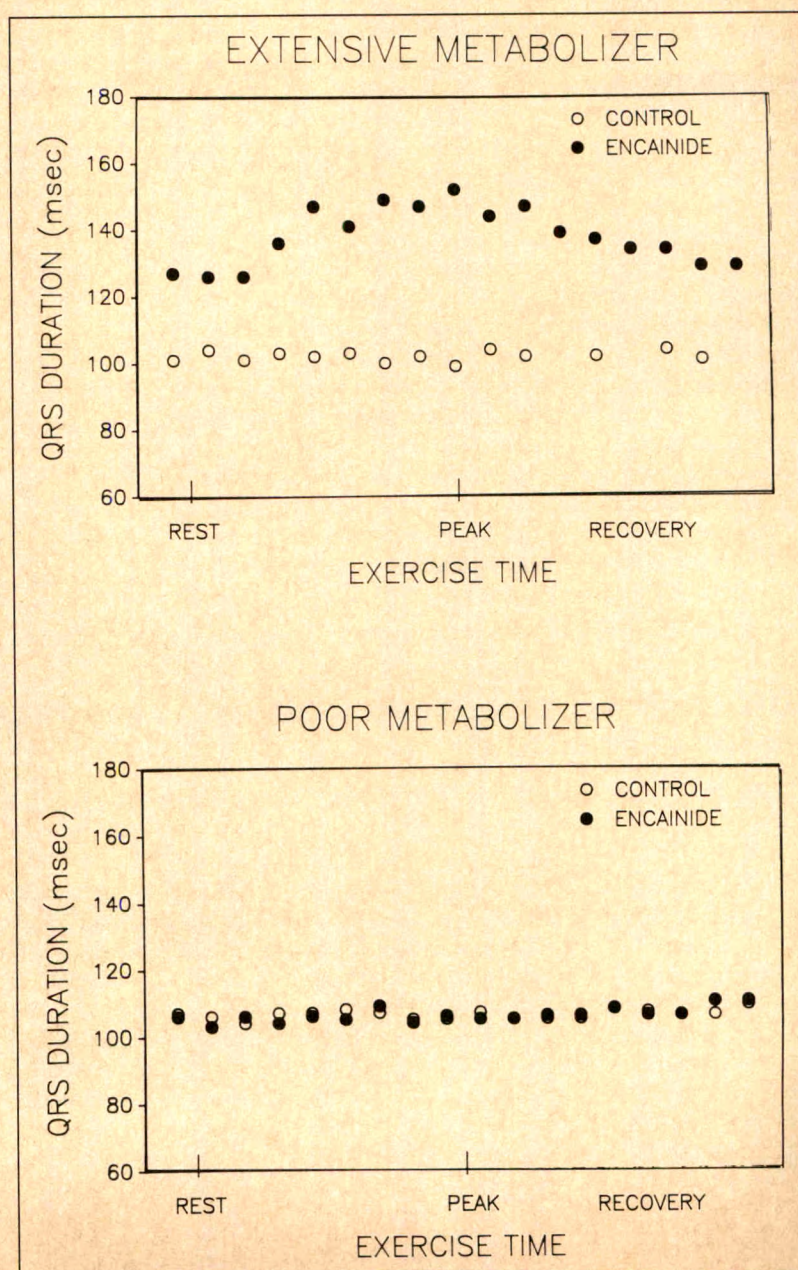
lizers, an increase in resting QRS duration was detected with encainide, with a mean increase in all 7 patients of 21 ± 13 ms. The 3 patients who demonstrated the greatest percent increase in QRS duration at rest with encainide (44, 38 and 33%) also demonstrated the greatest degree of exercise-induced QRS prolongation (11, 15 and 25%), although there was no consistent correlation for the 7 patients. Neither poor metabolizer demonstrated QRS prolongation on the resting electrocardiogram.

Encainide can cause rate-dependent prolongation of conduction in isolated cardiac muscle preparations.³ However, encainide is much less potent than ODE or MODE in producing rate-dependent effects on intraventricular conduction.⁴ In the present study, neither of the 2 patients who were poor metabolizers demonstrated rate-dependent changes in QRS duration despite high levels of

encainide. It appears that in the usually prescribed doses the concentration of encainide is not sufficient to produce rate-dependent increases in QRS duration; the presence of its active metabolites is required. Furthermore, it is of interest that no rate-dependent QRS prolongation was evident in 1 poor metabolizer despite a serum concentration of 100 ng/ml of ODE. However, the total serum concentration of ODE and MODE metabolites in this patient was still less than it was in any extensive metabolizer, and apparently was less than the minimum level of metabolite concentration necessary to show rate-dependent prolongation of intraventricular conduction.

The changes in intraventricular conduction demonstrated in this study occurred in the absence of clinical or electrocardiographic evidence of exercise-induced ischemia, and in the absence of other drugs that might influence conduction intervals. Furthermore, none of the pa-

FIGURE 2. Representative plots of the QRS duration during exercise and recovery in an extensive metabolizer (top) and in a poor metabolizer (bottom) of encainide. Each patient served as their own control. Top, before treatment with encainide, the QRS duration was 101 ms and did not change with exercise. With encainide (75 mg/day), the resting QRS increased to 127 ms and progressively increased further to 152 ms at peak exercise. During recovery, the QRS duration progressively decreased to baseline measurements. Bottom, before treatment with encainide, the QRS duration was 107 ms and did not change with exercise. With encainide (105 mg/day), no further QRS prolongation occurred at rest or with exercise.



tients were receiving drugs, such as quinidine, that are capable of interfering with encainide metabolism.⁶

These data also confirm previous findings with flecainide, another potent class IC antiarrhythmic agent, in which conduction slowing was enhanced by exercise-induced sinus tachycardia or by ventricular pacing.⁷ In the flecainide study, the physiologic increase in heart rate associated with exercise was the major determinant of conduction slowing, and other factors associated with exercise were apparently not contributory. In addition, flecainide's effect on QRS prolongation at rest predicted further QRS prolongation with exercise.

The encainide metabolites, ODE and MODE, play an important role in drug effects at rest.⁸ However, what effect rate-dependent prolongation of intraventricular conduction by ODE and MODE has on either antiarrhythmic efficacy or proarrhythmia has still not been fully elucidated.

Rate-dependent conduction slowing by flecainide has been implicated as an arrhythmogenic mechanism in predisposed patients. Ranger et al⁷ speculated that in patients with preexisting areas of abnormal conduction, rate-dependent conduction slowing by flecainide could so alter conduction that sustained reentry in a potentially arrhythmogenic region could develop.

Encainide can produce a proarrhythmic effect in predisposed patients, both with exercise⁹ and at rest.¹⁰ Conceivably, the mechanism of proarrhythmia may involve rate-dependent conduction slowing by encainide metabolites, ODE and MODE. If so, then blunting rate-dependent conduction slowing may prevent proarrhythmia from developing. Recent evidence suggests that the proarrhythmic effects of encainide and flecainide may be reversed by β -adrenergic blockade.¹¹ This is of particular interest in light of recent evidence from the Cardiac Arrhythmia Suppression Trial, which indicates that encainide can be deleterious in patients with asymptomatic postinfarction ventricular ectopy.¹²

Thus, in the quest for finding better ways of predicting drug efficacy, inefficacy and proarrhythmia, rate-related changes in QRS duration may be an additional means for evaluating drug effect. As indicated by these initial observations, rate-related changes in QRS duration may also be a means for recognizing subgroups of patients with different phenotypic patterns of encainide metabolism.

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Effects of Noninvasive Ambulatory Blood Pressure Measuring Devices on Blood Pressure

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It is well recognized that the act of blood pressure (BP) measurement may influence the level of BP.¹ This "cuff response" is attributed to an alerting reaction; it does not decrease with repeated measurement, and is worse in the presence of a doctor than in the presence of a nurse.² This suggests that the major component of the reaction is not discomfort from inflation of the cuff, and this is supported by the fact that BP usually increases before the cuff is applied. These observations have led to the assumption that ambulatory cuff BP devices do not

provoke such effects. This is implicit in the high reproducibility of measurements in groups of subjects that has been observed with some modern machines,³ although this could simply reflect the reproducibility of the alerting response. This issue has only been addressed in subjects confined to bed for relatively brief periods.⁴ No account has been taken of the possibility of effects on patients trying to sleep at night, or of the overall impact of wearing such devices. Ambulatory BP monitors are coming into wide use for the assessment of hypertensive subjects before and after treatment. This follows observations that ambulatory measurements are better prognostic indicators than casual readings.⁵ This study tests the hypothesis that wearing an ambulatory cuff BP monitor might, in itself, alter BP by increasing discomfort, influencing ac-

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tivity or sleep patterns, or by promoting an alerting response.

Thirteen patients (9 men and 4 women) undergoing ambulatory intraarterial BP monitoring for assessment of hypertension were studied. They had a mean age of 43 years (range 19 to 60). Of these subjects, 3 were taking medication: 2 were taking a slow-release preparation of nicardipine, and 1 was taking quinapril (a new angiotensin-converting enzyme inhibitor). Patients on β blockers were specifically excluded. All patients gave informed consent and the study was approved by the Harrow Health Authority Ethical Committee.

Initial 24-hour ambulatory intraarterial monitoring was performed without the addition of the cuff measuring device. The intraarterial recording was then continued for a further 24 hours after a Colin 630 noninvasive ambulatory BP monitor (Nippon/Colin, Japan) was attached.

The cuff of the Colin monitor was applied to the contralateral arm. This inflated 6 times per hour during the day and 3 times per hour during the night. During both monitoring periods, patients were fully ambulant outside the hospital, and were simply instructed to straighten and reduce arm movement to a minimum whenever the cuff device triggered. The pre-cuff inflation warning bleep was disabled. The device had a "retry" facility, so that if the patient moved the arm too vigorously during an inflation, a second inflation occurred.

Intraarterial BP monitoring was performed using the Oxford technique, which has been fully described and validated elsewhere.⁶ A 3Fr gauge Teflon[®] cannula was inserted into the brachial artery on the nondominant arm

under local anesthetic with the Seldinger technique, and was then connected to a transducer/perfusion unit through a manometer line; the signals from this and a bipolar electrocardiogram were recorded onto an Oxford Medilog 4-24 recorder, incorporating a time channel and electrical event marker.

The intraarterial BP tapes were replayed using an analog chart recorder to check for gross artifact or recorder malfunction. They were then analyzed with a purpose-built system consisting of a modified Reynolds Medical CR11 Holter cassette deck and a DEC MINC 11/23 digital computer. The timing was set up to align the digital clock of the Colin monitor with the intraarterial recording, and time correction was performed to account for tape speed variation. In no instance did this vary by >1 minute in 24 hours. In addition, the intraarterial BP signal was visually checked, for each patient, by an observer (PC), who tried to identify the points of cuff inflation from changes in intraarterial BP.

For each patient the 30-second mean intraarterial BP coincident with each cuff inflation was identified and compared with their residual overall mean daytime (midday to P.M. hours) and nighttime (midnight to 6 A.M. hours) BPs. Paired Student's *t* tests were performed

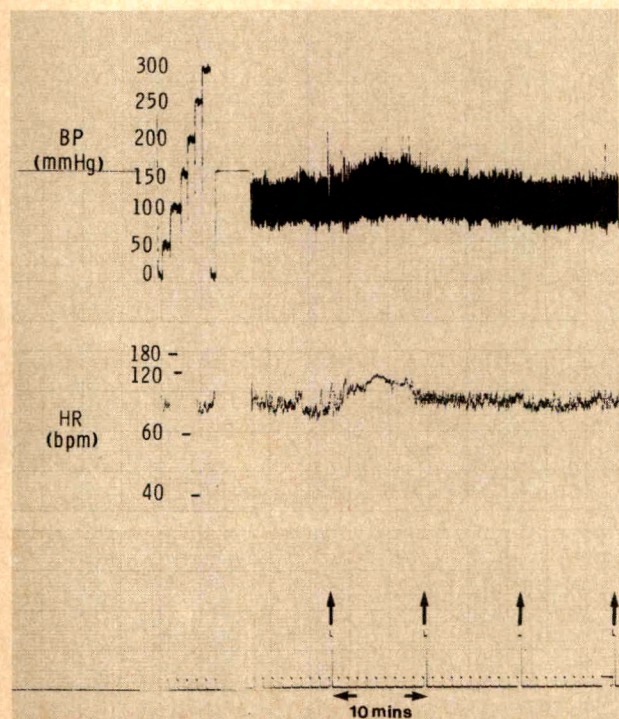


FIGURE 1. Part of an ambulatory recording of intraarterial blood pressure (BP) and heart rate (HR) with the points of cuff inflation indicated by arrows (10-minute intervals). The increase in BP coincided with activity and not with cuff inflation. bpm = beats/min.

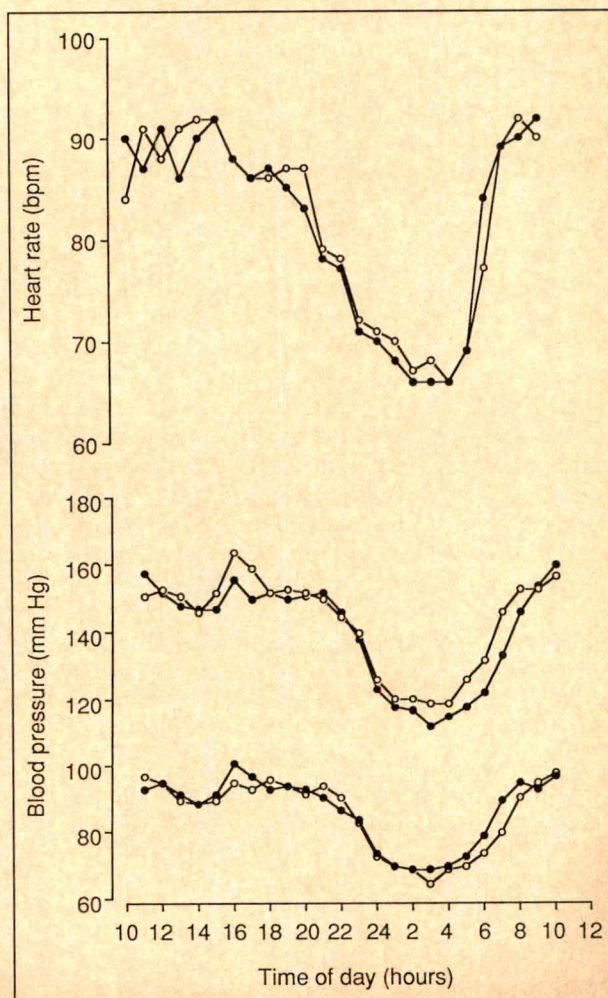


FIGURE 2. Twenty-four-hour profiles of intraarterial blood pressure and heart rate before (closed bullet) and after (open bullet) applying the noninvasive monitor.

TABLE I Number of Subjects Showing a Difference in Blood Pressure at Times of Inflation

	Day (Midday to 6 P.M.)			Night (Midnight to 6 A.M.)		
	Increase	Decrease	No Effect	Increase	Decrease	No Effect
Systolic pressure (mm Hg)	0	1 (5.7)	12	0	1 (1.7)	12
Diastolic pressure (mm Hg)	0	0	13	0	0	13
Heart rate (beats/min)	0	1 (5.9)	12	0	1 (3.4)	12

Numbers of subjects showing any significant effect (i.e., no effect indicates $p > 0.05$) on 30-second mean intraarterial blood pressure at times of inflation compared with the residual mean. The only significant changes occurred in 4 different subjects. The magnitudes of these changes are shown in brackets—all were decreases rather than increases.

for each patient to see if any significant changes in BP or heart rate had occurred. A 30-second mean intraarterial BP might be expected to coincide with the systolic and diastolic points of a cuff inflation, because it has been previously shown that brief (e.g., 1 minute) intraarterial BP means do not differ significantly from randomly selected single beats from within that period.⁷

Pooled mean hourly intraarterial BP and heart rate for all subjects were obtained for each hour of the 24-hour period before application of the Colin device. These were plotted for comparison with pooled mean hourly intraarterial BP and heart rate during the 24 hours of cuff BP monitoring to assess any overall impact of wearing the device. Significance was assessed using paired Student's *t* tests.

Inspection of the intraarterial BP signal as it was replayed did not reveal any recurring pattern of BP elevation that could be distinguished from normal variation (Figure 1). The patients did, however, show an increase in BP coincident with returning to the hospital to see the physician in the late afternoon (Figure 2).

Table I lists the numbers of subjects showing significant differences between their 30-second mean intraarterial BP at the times of cuff inflation and their residual means (each taken as a constant) for the daytime and nighttime periods. Only inflations that could be timed precisely were used (thus, failed inflations and "retries" were excluded), so that during the day these were based on a mean of 27 readings per patient and at night on a mean of 16 readings per patient. The only significant changes were small decreases in systolic BP and heart rate in 4 different subjects, suggesting that there were no pressor effects at the times of inflation, and that reduced activity at the points of inflation did not influence the results.

The pooled mean hourly intraarterial BP for the 2 consecutive 24-hour periods are shown in Figure 2. Overall, it can be seen that there was little difference between them. The characteristic BP increase at 17:00 hours (5 P.M.) coincided with the patients returning to the hospital for equipment checks by the physician. At this point, the intraarterial systolic BP was higher ($p < 0.05$) on the second day. The slightly higher nocturnal systolic BP suggested poorer sleep, but there was no significant difference in mean nighttime BP between the 2 monitoring periods.

This study demonstrates that ambulatory cuff BP devices do not induce a pressor response at the times of inflation. This applies both to the daytime period, when the patients were active and alert, and to the nighttime, when there might have been transient disturbances in sleep, with the potential for larger increases from basal measurements. This concurs with a recent report by Schwan and Pavlek,⁸ who suggested that basal nocturnal BP was not influenced by a bedside noninvasive device, despite evidence of transient sleep disturbance on the electroencephalogram. Thus, the concept of "white coat" rather than "cuff" hypertension gains additional support from these findings. The main implication is that, in common with intraarterial BP monitoring, ambulatory cuff monitors may be used with confidence, both clinically and in the context of drug trials, to exclude subjects who show an exaggerated BP response when visiting the doctor for casual cuff measurements. It also goes some way to explain why a technique of questionable accuracy^{9,10} has been shown to be reproducible in groups of subjects.

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STYLE: Use appropriate subheadings throughout the body of the text, such as the Methods, Results and Discussion. Tables, figures and references should be mentioned in numerical order throughout manuscript. Abbreviations are permitted, but no more than 3 per manuscript, and then they must be used on every page of the manuscript after they are initially spelled out (followed by the abbreviation) in both abstract and introduction. Abbreviations are usually limited to terms in the manuscript's title. Use generic names of drugs. Do not spell out any number, including those less than 10, except when used for opening a sentence, but try not to begin sentences with numbers. Use symbols for less than (<), greater than (>) and percent (%). Indent for paragraphs except the first one in both abstract and introduction. Consult the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, published in *The Annals of Internal Medicine* June 1982;96:766-771, and also the *Stylebook/Editorial Manual of the AMA*.

REFERENCES: List all authors, year, volume and inclusive pages for all journal references, and specific page numbers for all book references as shown below. Avoid referencing abstracts, but if they are used, indicate them as such by the abbreviation (abstr) after the title. Do not use periods after authors' initials or after abbreviations for titles of journals. Check *Index Medicus* or *Annals of Internal Medicine* (June 1982) as cited above for journal titles and abbreviations. Personal communications, unpublished observations and manuscripts submitted but not yet accepted for publication do not constitute references.

Journal: Harvey W, Heberden W, Withering W, Stokes W, Murrell W, Einthoven W, Osler W. Anomalies and curiosities of cardiology and of cardiologists. Reflections of famous medical Williams. *Am J Cardiol* 1984;53:900-915.

Chapter in Book: Cabot RC, White PD, Taussig HB, Levine SA, Wood P, Friedberg CK, Nadas AS, Hurst JW, Braunwald E. How to write cardiologic textbooks. In: Hope JA, ed. *A Treatise on Disease of the Heart and Great Vessels*. London: Yorke Medical Books, 1984:175-200.

Book: Carrel A, Cutler EC, Gross RE, Blalock A, Crafford C, Brock RC, Bailey CP, DeBakey ME. The Closing of Holes, Replacing of Valves and Inserting of Pipes, or How Cardiovascular Surgeons Deal with Knives, Knives and Knots. New York: Yorke University Press, 1984:903.

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Training for Intermediate Clinical Lipid Specialists

Most efforts to educate physicians about lipid disorders, such as the National Cholesterol Education Program, target all physicians, with emphasis on those providing primary care. There remains, however, a gap in lipid practice between the community physician engaged in primary care and the lipid specialist practicing at a tertiary referral center. Although the majority of patients with high cholesterol or triglyceride levels can be managed readily by the primary care physician, the remaining cases still exceed the capacity of the 50 or so regional lipid clinics in the United States.

To fill this gap, local community expertise in lipid disorders needs to be developed. The concept of the intermediate clinical lipid specialist has emerged—a physician who can serve as a resource for consultation and who can establish a standard of practice as an opinion leader in large and small communities. A new training program in lipid disorders initiated by the American Heart Association (AHA) is intended to help to meet this need.

Six regional lipid clinics were chosen as AHA Training Centers for Clinical Management of Lipid Disorders on the basis of peer-reviewed competitive applications and are to be funded by an educational grant from Bristol Myers-Squibb. Each center will provide in-depth education in pathophysiology, diagnosis and management of a wide spectrum of lipoprotein disorders to approximately 80 physicians per year. The trainee will be expected to undertake home study as well as a 3- to 5-day intensive on-site course. The educational experience will involve didactic course material, laboratory experience, nutrition counseling, practical "hands-on" examination of patients, case study discussions and practice management seminars under the personal tutelage of a highly qualified faculty of lipid specialists. Each physician trainee will be encouraged to bring 1 or possibly more ancillary staff members, such as nurses and dietitians.

The follow-up component is perhaps most important for successful implementation of a community-based lipid specialist program. The 6 Training Centers, in connection with other major referral lipid clinics, will continue to serve as tertiary referral centers for difficult cases. In addition, plans for telephone or facsimile consultation services are being developed. The centers will serve as, or be associated with, laboratory referral sites for compar-

ison with local laboratories and for provision of lipoprotein tests not commonly available in community laboratories. An annual 1-day continuing education conference for course graduates and a newsletter are also planned.

Practicing physicians who have the opportunity to serve as lipid consultants in their communities are encouraged to apply. Specialization will not be a selection criteria, although a significant amount of the physician's time should be spent in direct patient care. Selection of trainees will be based in part on regional distribution.

Training Centers are located at Baylor College of Medicine, Houston, Texas; Johns Hopkins University, Baltimore, Maryland; University of California, San Francisco and Berkeley, California; University of Iowa, Iowa City, Iowa; University of Washington, Seattle, Washington; and Washington University, St. Louis, Missouri. The first courses are scheduled to begin in January 1991. For information and applications forms, write: Eleanor Sanders, Coordinator, AHA/Squibb Lipid Disorders Training Centers, American Heart Association, 7320 Greenville Avenue, Dallas, Texas 75231.

H. Robert Superko, MD
Berkeley, California

Ventricular Arrhythmias During Spontaneous Ischemic ST-Segment Depression

In the February 15, 1990 issue of *The American Journal of Cardiology*, we reported our observations on the association of ventricular arrhythmias and increased ventricular ectopic activity during ischemic episodes.¹ We believed it was important to emphasize even in the title of our report that we dealt with ambulatory patients. While our article was in press, the October 15, 1989 issue carried an article by Turitto et al² on their experience with ventricular arrhythmia "during spontaneous ischemic ST-segment depression." Only careful reading of the "Methods" section enabled us to realize that their investigation dealt exclusively with in-hospital patients, and that the reason for hospitalization in "all patients" (my emphasis) was "symptoms consistent with spontaneous angina . . ." This raises the possibility that many of them could have been diagnosed as having unstable angina. This seems to have been the case for the 28 patients with "recent onset" angina and for the 15 others (although these 2 groups may have overlapped) with "worsening" angina; the latter group may have included patients with "crescendo" pain, also classified by many as unstable angina. Only for 17 patients do the authors clarify that "angina was stable."

If, as seems to be true, quite a few of the patients included in the Turitto et al study had unstable angina, this could explain

the somewhat higher incidence of ventricular arrhythmias, as well as the more malignant types (ventricular tachycardias during 6 ischemic attacks) in their study than in the study we reported.

Shlomo Stern, MD
Jerusalem, Israel
31 January 1990

1. Stern S, Banai S, Keren A, Tzivoni D. Ventricular ectopic activity during myocardial ischemic episodes in ambulatory patients. *Am J Cardiol* 1990;65:412-416.

2. Turitto G, Zanchi E, Maddaluna A, Pellegrini A, Risa AL, Prati PL. Prevalence, time course and malignancy of ventricular arrhythmia during spontaneous ischemic ST-segment depression. *Am J Cardiol* 1989;64:900-904.

REPLY: We acknowledge differences in the incidence of ventricular arrhythmias during transient myocardial ischemia between our study¹ and the one by Stern et al.² As was correctly pointed out, the discrepancy may be due to different selections of the patient population. Stern et al focused on patients with stable angina, while we devoted our attention to patients with spontaneous ischemic ST depression, as was clearly stated in the title of our article.¹ We elected to use the definition "spontaneous angina" rather than "unstable angina" because we feel that the latter represents a mixed bag into which different categories of patients with exertional, spontaneous chest pain, or both, may fall.³

Our study unequivocally showed that the frequency of ventricular arrhythmias depends on the severity of myocardial ischemia.¹ In fact, the number of daily ischemic attacks and the total ischemic time doubled in the group with arrhythmias, as compared to the group without arrhythmias. Moreover, in patients with arrhythmias, ischemic attacks lasted twice as long in the presence of arrhythmias than they did in their absence. The characteristics of the overall population studied by Stern et al² were remarkably similar to those without arrhythmias documented in our group, as far as the number of ischemic attacks, total ischemic time and duration of ischemic attacks were concerned. Their finding of a lower arrhythmogenicity may thus be expected based on these data. On the other hand, the frequency of arrhythmias related to ischemic attacks may have been overestimated in their analysis, because the occurrence of frequent ventricular premature complexes unrelated to ischemic attacks did not represent an exclusion criterion in their study (mean ventricular premature complexes/24 hrs 243 ± 538). Their definition of "increased ventricular ectopic activity," which formed the basis for their diagnosis of arrhythmogenic ischemic attacks in all their patients, may not be entirely accurate, based on the spontaneous variability of ventricular arrhythmias.⁴

Gioia Turitto, MD
Wichita, Kansas
5 March 1990

Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

1. Turitto G, Zanchi E, Maddaluna A, Pellegrini A, Risa AL, Prati PL. Prevalence, time course and malignancy of ventricular arrhythmia during spontaneous ischemic ST-segment depression. *Am J Cardiol* 1989;64:900-904.
2. Stern S, Banai S, Keren A, Tzivoni D. Ventricular ectopic activity during myocardial ischemic episodes in ambulatory patients. *Am J Cardiol* 1990;65:412-416.
3. Rutherford JD, Braunwald E, Cohn PF. Chronic ischemic heart disease. In: Braunwald E, ed. *Heart Disease*. Philadelphia: WB Saunders, 1988:1314-1378.
4. Winkle RA, Peters F, Hall R. Characterization of ventricular tachyarrhythmias on ambulatory ECG recordings in post-myocardial infarction patients: arrhythmia detection and duration of recording, relationship between arrhythmia frequency and complexity, and day-to-day reproducibility. *Am Heart J* 1981;102:162-169.

Balloon Angioplasty of Native Aortic Coarctations

I read with interest the article entitled "Balloon Angioplasty for the Treatment of Native Coarctation: Results of Valvuloplasty and Angioplasty of Congenital Anomalies Registry" in the March 15th issue of *The American Journal of Cardiology*.¹ Because of my interest in balloon angioplasty of native aortic coarctations,²⁻⁹ I was hoping that a study involving as large a number of patients as this¹ would answer the questions and concerns that many cardiologists have, but I was disappointed to note that this article did not address these issues and that, in addition, problems with regard to data collection, analysis and interpretation exist. I am surprised at the incompleteness of the data; there were full data in only 92 of 141 procedures; even the dates of birth were not available in 29 procedures. Why was no attempt made to obtain this information before publication of this paper? How many of the patients reported on in this paper were previously reported? From the list of the participating institutions,¹⁰ one can easily surmise that many of these patients had been previously reported. It was stated that aneurysms were confirmed in 7 children and suspected in

1, giving an incidence of 5 to 6%. Was there follow-up in all 140 patients? I thought that the authors stated elsewhere in the paper that there was no follow-up data. If there was no follow-up data, how was the percent incidence derived? If there was follow-up, did all these patients have follow-up catheterization and angiography (or magnetic resonance imaging) and, if so, what were the residual gradients? How many had recoarctation?

When considering the effect of the ratio of balloon diameter to coarctation diameter on the residual pressure gradient, it may have been worthwhile to look at residual gradients at varying levels of balloon/coarctation diameter ratios.

Finally, the conclusion of this article¹ was, "The question remains not can it be done, but should it be done?", whereas the article on balloon angioplasty of aortic recoarctation after previous surgery¹¹ concludes, "... balloon angioplasty for relief of residual or recurrent aortic coarctation offers an acceptable alternative to repeat surgical repair." If one examines the results of both studies (Table I), the degree of gradient relief and the arterial complication rate are similar for both native coarctations and recoarctations.^{1,11} However, the death rate after angioplasty is slightly higher for recoarctations (2.5%, 5 of 200) than that for native coarctations (0.7%, 1 of 141), although this did not attain statistical significance (p is between 0.05 and 0.1). I wonder about the objectivity of the scientific interpretation; how can one conclude almost the opposite with exactly similar data? With these data and other data collected from previously published reports that we tabulated elsewhere,⁷ one cannot recommend balloon angioplasty for recoarctation while not recommending it for native coarctation. I do believe that we need to maintain objectivity of scientific interpretation and perhaps wait for long-term follow-up results on a larger number of patients in both native and recoarctation groups to become available before making any definitive recommendations.

P. Syamasundar Rao, MD
Madison, Wisconsin
16 April 1990

1. Tynan M, Finley JP, Fontes V, Hess J, Kan J. Balloon angioplasty for the treatment of native coarctation: results of valvuloplasty and angioplasty of congenital anomalies registry. *Am J Cardiol* 1990;65:790-792.
2. Rao PS, Mardini MK, Najjar HN. Relief of coarctation of the aorta without thoracotomy: the experience with percutaneous balloon angioplasty. *Ann Saudi Med* 1986;6:193-203.
3. Rao PS. Transcatheter treatment of pulmonary stenosis and coarctation of the aorta: experience with percutaneous balloon dilatation. *Br Heart J* 1986;56:250-258.
4. Rao PS. Balloon angioplasty for coarctation of the aorta in infancy. *J Pediatr* 1987;110:713-718.
5. Rao PS, Najjar HN, Mardini MK, Solyman L, Thapar MK. Balloon angioplasty for coarctation of the aorta: immediate and long-term results. *Am Heart J* 1988;115:657-664.
6. Rao PS, Thapar MK, Kutayli F, Carey P. Causes of recoarctation following balloon angioplasty of unoperated aortic coarctations. *J Am Coll Cardiol* 1989;13:109-115.
7. Rao PS. Which aortic coarctation should we balloon dilate? (editorial) *Am Heart J* 1989;117:987-989.
8. Rao PS, Carey P. Remodeling of the aorta following successful balloon coarctation angioplasty. *J Am Coll Cardiol* 1989;14:1312-1317.
9. Rao PS. Balloon angioplasty of aortic coarctation: a review. *Clin Cardiol* 1989;12:618-628.
10. Allen HD, Mullins CE. Results of the valvuloplasty and angioplasty of congenital anomalies registry. *Am J Cardiol* 1990;65:772-774.
11. Hellenbrand WE, Allen HD, Golinko RJ, Hagler DJ, Lutin W, Kan J. Balloon angioplasty of aortic recoarctation: results of valvuloplasty and angioplasty of congenital anomalies registry. *Am J Cardiol* 1990;65:793-797.

Postmortem Cardiomyopathy or Postpartum Cardiomyopathy?

Recently a medical student on ward rounds presented to me a woman who developed congestive heart failure 2 days after her delivery of a full-term baby. In the chart the student wrote that the patient was suffering from "postmortem cardiomyopathy." I knew that postpartum cardiomyopathy was pretty serious, but did not think it was that serious. At long last, you as a pathologist and I as a cardiologist find we have something in common.

Tsung O. Cheng, MD
Washington, D.C.
27 August 1990

CORRECTION

In an August 1, 1990 editorial, "Rationale Against the Drug Treatment of Marginal Diastolic Systemic Hypertension," by Freis, the legend for Figure 1 on page 369 incorrectly attributes the figure to tabular data drawn from Cruikshank et al.¹⁰ The figure is actually drawn from tabular data presented by McGee et al.⁸

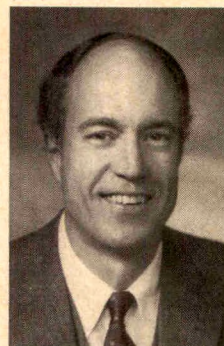
TABLE I Comparison of Results of Balloon Angioplasty from VACA Registry

	Native Coarctation ¹	Recoarctation ¹¹	p Value
Pressure gradient relief			
Before angioplasty	48 ± 19*	42 ± 20*	>0.1
After angioplasty	12 ± 11*	9 ± 3*	
Arterial complications	14/114 (9.9%)	17/200 (8.5%)	>0.1
Deaths	1/141 (0.7%)	5/200 (2.5%)	0.05-0.1

* mm Hg; mean ± standard deviation.
VACA = Valvuloplasty and Angioplasty of Congenital Anomalies.

The Best Antiarrhythmic Agent Will Be a Lipid-Lowering Agent

In September 1990 I attended a 2-day conference on Sudden Cardiac Death and heard a number of talks on malignant and potentially malignant ventricular arrhythmias. A variety of cardiac conditions, of course, have an increased propensity to develop ventricular arrhythmias. These include coronary artery disease, systemic hypertension, idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, amyloidosis, sarcoidosis, mitral valve prolapse, some congenital cardiac anomalies, among others, and occasionally some malignant arrhythmias develop in the absence of "structural heart disease." Although they may be associated with several conditions, malignant ventricular arrhythmias most commonly (>75%) occur in association with severe coronary arterial narrowing from atherosclerosis. And the frequency of symptomatic and fatal myocardial ischemia increases as the amount of atherosclerotic plaque in our coronary arteries increases. And the amount of plaque increases as our total and low-density lipoprotein cholesterol levels in the serum increase and as the high-density lipoprotein cholesterol level decreases. If the percentage of calories from fat diminished in our diets from 40–42% to about 10%, our serum total cholesterol levels and the frequency of symptomatic and fatal myocardial ischemia would drop to rates where malignant ventricular arrhythmias would be "non-problems." Because reducing our percentage of calories from fat by 75% is unrealistic for most of us, the lipid-lowering drugs are needed.



In conjunction with low fat-low cholesterol diets, lipid-lowering agents slow, retard and reverse the atherosclerotic process, and, therefore, delay, retard and prevent the formation of atherosclerotic plaques by lowering our total and low-density lipoprotein serum levels, and by raising our high-density lipoprotein levels. The lower the total and low-density lipoprotein levels, the less the atherosclerotic plaque and the less the chance of developing malignant and potentially malignant arrhythmias.

I kept wondering during the sudden-cardiac-death conference how much the cardiac electrical experts knew or cared about cholesterol. I'll wager a bet with anyone that lipid-lowering agents eventually will prove to be the best antiarrhythmic agents.

William C. Roberts

William Clifford Roberts, MD

The American Journal of Cardiology

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DECEMBER 15, 1990

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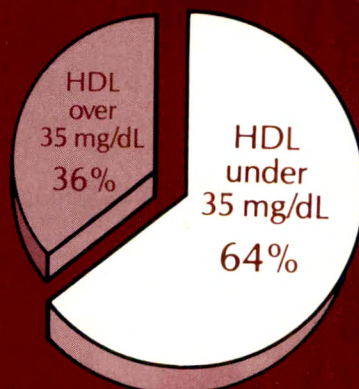
<35 HDL

mg/dL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,¹ and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.²

HEART ATTACK PATIENTS
(PROCAM TRIAL)²



CORONARY ARTERY DISEASE**1403****Changes in Myocardial Ischemic Threshold During Daily Activities**

Shmuel Banai, Mady Moriel, Jesaia Benhorin, Alex Gavish, Shlomo Stern, and Dan Tzivoni

We studied myocardial ischemic thresholds (heart rate at the onset of ischemic episodes) in 80 patients with coronary artery disease and observed marked variability of ischemic thresholds in different patients. The highest ischemic threshold during daily activities was similar to that during exercise and may represent an impairment in coronary blood flow due to a fixed coronary lesion, whereas the lowest ischemic threshold probably represents a reduction in flow due to increased coronary tone.

1407**Changes in Standard Electrocardiographic ST-Segment Elevation Predictive of Successful Reperfusion in Acute Myocardial Infarction**

Peter Clemmensen, E. Magnus Ohman, Dorina C. Sevilla, Steve Peck, Nancy B. Wagner, Peter S. Quigley, Peer Grande, Kerry L. Lee, and Galen S. Wagner

The sum of ST-segment elevation in affected electrocardiographic leads was compared before and after thrombolytic therapy in 53 patients with acute myocardial infarction. Investigation revealed that a 20% decrease in ST elevation provided a diagnostic test with simultaneous high sensitivity, specificity and positive predictive value. Results confirm the usefulness of the standard electrocardiographic ST segment as a noninvasive predictor of reperfusion.

1412**Effect of Heparin on Coronary Arterial Patency After Thrombolysis with Tissue Plasminogen Activator in Acute Myocardial Infarction**

Stanley D. Bleich, Timothy C. Nichols, Richard R. Schumacher, David H. Cooke, David A. Tate, and Sam L. Teichman

Eighty-four patients with acute myocardial infarction received a standard dose of 100 mg of recombinant tissue-type plasminogen activator over 3 hours and 42 of these were immediately administered intravenous heparin anticoagulation. Data indicate that after rt-PA therapy, heparin is associated with substantially higher coronary patency rates 3 days after thrombolysis but is accompanied by an increased incidence of minor bleeding complications.

1418**Usefulness of a Pericardial Friction Rub After Thrombolytic Therapy During Acute Myocardial Infarction in Predicting Amount of Myocardial Damage**

Thomas C. Wall, Robert M. Califf, Lynn Harrelson-Woodlief, Daniel B. Mark, Michael Honan, Charles W. Abbottsmith, Richard Candela, Eric Berrios, Harry R. Phillips, Eric J. Topol, and the TAMI Study Group

We prospectively studied 810 patients who developed a pericardial friction rub after receiving thrombolytic therapy for acute myocardial infarction to evaluate clinical incidence and outcomes. Although the incidence of clinical pericarditis in this setting is low (5%), patients with this complication have more extensive myocardial damage and a higher in-hospital mortality, but do not develop cardiac tamponade.

1422**Determinants and Significance of Diltiazem Plasma Concentrations After Acute Myocardial Infarction**

Stanley Nattel, Mario Talajic, Robert E. Goldstein, John McCans, and The Multicenter Diltiazem Postinfarction Trial Research Group

In 1,067 patients studied in the Multicenter Diltiazem Postinfarction Trial, we sampled 1,975 plasma drug concentrations at 1-, 6-month and closeout intervals and found them significantly affected by drug dose actually taken, time from the last dose, patient age and height, and left ventricular dysfunction as indicated by pulmonary edema on x-ray. Diltiazem's effects depend on its concentration in blood plasma, and consideration of patient age, size and left ventricular function may allow for benefit with a reduced risk of adverse effects.

1429**Prehospital Thrombolysis in Acute Myocardial Infarction**

Joachim Schofer, Jochen Büttner, Gabriele Geng, Klaus Gutschmidt, Hans N. Herden, Detlef G. Mathey, Heinz P. Moecke, Peter Polster, Alexander Raftopoulos, Florence H. Sheehan, and Peter Voelz

The benefit and risk of prehospital thrombolysis for acute myocardial infarction were evaluated in a double-blind randomized trial. Prehospital thrombolysis using a bolus injection of urokinase has a low risk when performed by a trained physician with a mobile care unit. The saving of 45 minutes in the early stage of an acute infarction through prehospital thrombolysis did not appear important for salvage of myocardial function.

1434

Acute Myocardial Infarction and Chest Pain Syndromes After Cocaine Use

Mahesh Amin, Gary Gabelman, Jill Karpel, and Peter Buttrick

We evaluated 70 patients hospitalized with chest pain after cocaine use to define risk and clinical course of acute myocardial infarction. AMI may not be due to primary effects of cocaine but rather its secondary effects leading to gradual thrombus formation. Median time to onset of chest pain after cocaine ingestion was longer in patients who developed AMI than in those who did not.

1438

Comparison of Thallium-201 and Technetium-99m Hexakis 2-Methoxyisobutyl Isonitrile Single-Photon Emission Computed Tomography for Estimating the Extent of Myocardial Ischemia and Infarction in Coronary Artery Disease

Kenneth A. Narahara, Javier Villanueva-Meyer, Craig J. Thompson, Marianne Brizendine, and Ismael Mena

Single-photon emission computed tomography using thallium-201 was compared with technetium-99m hexakis 2-methoxyisobutyl isonitrile in 24 patients with coronary artery disease. Defect size estimated from stress Tl-201 images was significantly larger than the exercise Tc-99m MIBI estimates of defect mass. Stress Tc-99m MIBI defect sizes defined by visual interpretation or use of isocount analysis may be smaller than those obtained with stress Tl-201 SPECT.

1445

Recanalization of Chronic Total Coronary Arterial Occlusions by Percutaneous Excimer-Laser and Laser-Assisted Angioplasty

Gerald S. Werner, Arnd Buchwald, Christina Unterberg, Eberhard Voth, Heinrich Kreuzer, and Volker Wiegand

Recanalization was attempted by excimer laser angioplasty in 39 patients with a chronic coronary occlusion. After passing the occlusion by a wire in 27 patients, the laser catheter could be advanced across the occlusion in 25 patients. If the residual stenosis exceeded 50%, laser was followed by additional balloon angioplasty. Primary success was limited by the need for a successful passage of the wire; limited size of the achieved lumen required additional balloon angioplasty in 76% of cases.

1451

Prevalence and Prognostic Significance of Exercise-Induced Ventricular Arrhythmias After Coronary Artery Bypass Grafting

Sinikka Yli-Mäyry, Heikki V. Huikuri, Ulla R. Korhonen, K.E. Juhani Airaksinen, Markku J. Kälheimo, Markku K. Linnaluoto, and Juha T. Takkanen

Two hundred patients who were studied before and 3 months after coronary artery bypass grafting were prospectively followed up for 61 ± 19 months. The prevalence of exercise-induced ventricular arrhythmias increases after CABG, but the occurrence of ventricular arrhythmias does not indicate an increased risk of cardiac death.

1455

Temporal Relation Between Left Ventricular Dysfunction and Chest Pain in Coronary Artery Disease During Activities of Daily Living

Junichi Taki, Tsunehiro Yasuda, Nagara Tamaki, Scott D. Flamm, Adolph Hutter, Herman K. Gold, Robert Leinbach, and H. William Strauss

To determine the incidence and temporal sequence of left ventricular dysfunction, ST-segment depression and chest pain onset in patients with documented coronary artery disease, we monitored 43 patients for 2.9 ± 1.9 hours with an ambulatory LV monitoring device that couples radionuclide techniques with Holter monitoring, providing a beat-by-beat description of cardiac function and electrocardiographic changes during daily activities. Our data suggest that LV dysfunction manifested by a decrease in ejection fraction precedes angina pectoris or electrocardiographic evidence of myocardial ischemia.

1459

Recanalization of Chronic, Totally Occluded Coronary Arteries by New Angioplasty Systems

Christian W. Hamm, Wolfram Kupper, Karl-Heinz Kuck, Dirk Hofmann, and Walter Bleifeld

We evaluated new angioplasty devices in 154 consecutive patients with chronic total coronary occlusions, following a stepwise design in which conventional guidewires and low-profile balloons were followed by "balloon-on-the-wire" systems or by a shaft-enforced, tip-deflecting catheter. An 82% success rate was achieved in patients with total occlusions of <12 weeks' duration and a 58% success rate in arteries occluded from 3 to 12 months. When occlusions were older than 3 months, 37% of lesions were managed only by the advanced, not the conventional equipment, with a low complication rate. These results support the observation that duration of the occlusion is a key determinant for successful recanalization.

1464

Low-Dose Aspirin Versus Anticoagulants for Prevention of Coronary Graft Occlusion

Michael A. J. Weber, Joerg Hasford, Claude Tailens, Alexander Zitzmann, Georg Hahalis, Herbert Seggewiss, Axel F. Langbehn, Dieter Fassbender, Rainer Buchwalsky, Karl Theisen, and Eric Hauf

The prevention of graft occlusion by aspirin or heparin followed by phenprocoumon was investigated in a randomized trial in 235 patients after aortocoronary bypass operation. Because occlusion rates were equal but high in patients with advanced coronary artery disease, a combination of low-dose aspirin and anticoagulant therapy should be investigated to reduce graft occlusion rates further.

SYSTEMIC HYPERTENSION

1469

Arterial Vasodilator Effects of the Dihydropyridine Calcium Antagonist Amlodipine Alone and in Combination with Verapamil in Systemic Hypertension

Wolfgang Kiowski, Paul Erne, Lilly Linder, and Fritz Rolf Bühler

The arterial vasodilator properties of the dihydropyridine calcium antagonist amlodipine were compared with the vascular effects of sodium nitroprusside and with the combined infusion of amlodipine and the nondihydropyridine calcium antagonist verapamil in 8 untreated patients with primary hypertension. Forearm blood flow increased dose dependently during graded brachial artery amlodipine infusions, whereas sodium nitroprusside resulted in less of an increase; combined infusion of amlodipine and verapamil resulted in an additional significant increase of forearm blood flow above that seen with amlodipine alone.

CARDIOMYOPATHY

1473

Left Ventricular Filling Impairment in Asymptomatic Chronic Alcoholics

Markku Kupari, Pekka Koskinen, Antti Suokas, and Markku Ventilä

Using M-mode and Doppler echocardiography to study left ventricular size, mass, systolic function and diastolic filling, we compared 32 alcoholics free of heart disease with 15 healthy control subjects and found that alcoholics have a higher wall thickness and mass of the left ventricle, as well as a prolonged relaxation time, lower peak velocity and acceleration of the early flow, and a higher atrial-to-early peak velocity ratio. These findings suggest that impairment of early diastolic filling due to delayed relaxation is an early sign of preclinical alcoholic cardiomyopathy.

CONGENITAL HEART DISEASE

1478

Physiologic Peripheral Pulmonic Stenosis in Infancy

Ricardo J. Rodriguez and Thomas W. Riggs

We examined 14 premature infants with peripheral pulmonic stenosis and 15 full-term neonates by Doppler echocardiography. The PPS group had smaller branch pulmonary artery diameters and greater peak velocities in the main PA. Thus, patients with PPS have mild underdevelopment of the PA branches, with consequent increased flow velocity and turbulent flow.

1482

Coronary Arteries in Truncus Arteriosus

Maria V. de la Cruz, Raul Cayre, Paolo Angelini, Nicholas Noriega-Ramos, and Stanislaw Sadowinski

The origin and distribution of the coronary arteries was described in 39 autopsy specimens of truncus arteriosus classified according to the number and patterns of truncal cusps with positions defined in relation to the atrioventricular orifices. Great variation in the origin and proximal course of the coronary arteries was observed.

MISCELLANEOUS

1487

Spectrum of Hemodynamic Changes in Cardiac Tamponade

P. Sudhakar Reddy, Edward I. Curtiss, and Barry F. Uretsky

To investigate the pathophysiology of cardiac tamponade, the hemodynamic changes of 77 consecutive patients with >150 ml of pericardial effusion were studied. Hemodynamic abnormalities, including the inspiratory decrease in arterial systolic pressure, progressively increased with increasing accumulation of pericardial effusion. Thus, the hemodynamic changes induced by pericardial effusion are a continuum and cardiac tamponade is not an all-or-none phenomenon.

1492

Transesophageal Echocardiography in Critically Ill Patients

Jae K. Oh, James B. Seward, Bijoy K. Khandheria, Bernard J. Gersh, Christopher G.A. McGregor, William K. Freeman, Lawrence J. Sinak, and A. Jamil Tajik

Transesophageal echocardiography was performed in 51 critically ill patients in the intensive care unit. In 59% of patients, this method identified cardiovascular problems that

could not be clearly diagnosed by transthoracic echocardiography. Transesophageal echocardiography, a unique extension of the echocardiographic technique, is safe and has an expanding role in the management of critically ill patients suspected of having cardiovascular compromise.

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1496

The Developmental Phase of Modern Coronary Artery Surgery

René Gerónimo Favaloro

In this anecdotal history of a landmark era in the development of modern coronary artery surgery, the author reconstructs the Cleveland Clinic cardiovascular team's contributions to myocardial revascularization, paying special homage to the memory of his friend, Dr. Mason Sones.

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CORONARY ARTERY DISEASE

1403**Changes in Myocardial Ischemic Threshold During Daily Activities**

Shmuel Banai, Mady Moriel, Jesaia Benhorin, Alex Gavish, Shlomo Stern, and Dan Tzivoni

Changes in myocardial ischemic threshold (heart rate at the onset of ischemic episodes) were assessed in 80 patients with known coronary artery disease and with ischemic changes during daily activities as recorded by ambulatory electrocardiographic monitoring. Variability in ischemic threshold increased with the number of ischemic episodes (range 2 to 60%). However, in different patients with a similar number of ischemic episodes, different variability was observed. These differences in ischemic threshold probably represent the vasomotor activity of the coronary arteries in different patients. The highest ischemic threshold during daily activities was similar to the ischemic threshold during exercise and probably represents an impairment in coronary blood flow due to a fixed coronary lesion, whereas the lowest ischemic threshold probably represents the reduction in flow due to increased coronary tonus.

1407**Changes in Standard Electrocardiographic ST-Segment Elevation Predictive of Successful Reperfusion in Acute Myocardial Infarction**

Peter Clemmensen, E. Magnus Ohman, Dorina C. Sevilla, Steve Peck, Nancy B. Wagner, Peter S. Quigley, Peer Grande, Kerry L. Lee, and Galen S. Wagner

This study compared the sum of ST-segment elevation in the standard electrocardiogram on admission and before acute cardiac catheterization in 53 patients to examine which amount of ST change best predicted infarct artery reperfusion. After thrombolytic therapy, 33 patients had successful reperfusion and 20 patients had occluded infarct arteries. Logistic regression analysis showed that the proportional value for the shift in the sum of ST elevation was a stronger predictor of reperfusion than the absolute difference measured in millimeters (chi-square = 11.34). Investigation of the entire spectra of sensitivities and specificities revealed that a decrease of 20% in ST elevation provided a diagnostic test with simultaneous high sensitivity, specificity (88 and 80%, respectively) and positive predictive value (88%). These results confirm the usefulness of the standard electrocardiographic ST segment as a noninvasive predictor of reperfusion.

1412**Effect of Heparin on Coronary Arterial Patency After Thrombolysis with Tissue Plasminogen Activator in Acute Myocardial Infarction**

Stanley D. Bleich, Timothy C. Nichols, Richard R. Schumacher, David H. Cooke, David A. Tate, and Sam L. Teichman

The contribution of heparin to efficacy and safety after thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) is unknown. In this pilot study, 84 patients with acute myocardial infarction received the standard dose of 100 mg of rt-PA over 3 hours and 42 of these were immediately administered intravenous heparin anticoagulation. Coronary angiography at a mean of 57 hours after rt-PA therapy revealed infarct artery patency rates of 71 and 43%, in anticoagulated and control patients, respectively ($p = 0.015$). Recurrent ischemia or infarction, or both, occurred in 3 (7.1%) anticoagulated patients and in 5 (11.9%) control patients (difference not significant). Mild, moderate and severe bleeding occurred in 52, 10 and 2% of the anticoagulated group, respectively, and in 34, 2 and 0% of control patients, respectively ($p = 0.006$). After rt-PA therapy for acute myocardial infarction, anticoagulation is associated with substantially higher coronary patency rates 2 to 3 days after thrombolysis but is accompanied by an increase in minor bleeding complications.

1418**Usefulness of a Pericardial Friction Rub After Thrombolytic Therapy During Acute Myocardial Infarction in Predicting Amount of Myocardial Damage**

Thomas C. Wall, Robert M. Califf, Lynn Harrelson-Woodlief, Daniel B. Mark, Michael Honan, Charles W. Abbot-Smith, Richard Candela, Eric Berrios, Harry R. Phillips, Eric J. Topol, and the TAMI Study Group

To evaluate the clinical incidence and outcomes of patients who developed a pericardial friction rub after receiving thrombolytic therapy for acute myocardial infarction, 810 patients were prospectively studied. Only 5% of all patients developed clinical pericarditis. Patients with a pericardial rub experienced more severe myocardial damage with significantly worse global and regional wall left ventricular function. Mortality was higher in patients with a rub (15%) compared with those without this complication (6%). No patient with a pericardial rub developed cardiac tamponade during hospitalization. Although the incidence of clinical pericarditis in this setting is low (5%), patients with this complication have more extensive myocardial damage and a higher in-hospital mortality, but do not develop cardiac tamponade.

1422**Determinants and Significance of Diltiazem Plasma Concentrations After Acute Myocardial Infarction**

Stanley Nattel, Mario Talajic, Robert E. Goldstein, John McCans, and The Multicenter Diltiazem Postinfarction Trial Research Group

The determinants of diltiazem concentrations and their clinical consequences were evaluated, using 1,975 plasma drug concentrations from 1,067 patients measured in the Multicenter Diltiazem Postinfarction Tri-

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al. Diltiazem concentrations were significantly affected by the drug dose taken, time from the last dose, patient age and height, and the presence of left ventricular dysfunction as indicated by radiologic evidence of pulmonary edema. Total body weight and dose prescribed were not important determinants of drug concentration. Diltiazem concentrations were highly significant determinants of diastolic arterial pressure ($p < 10^{-9}$), of the occurrence of atrioventricular block ($p = 0.02$), and of the need for temporary pacemaker therapy ($p = 0.02$). This study suggests that diltiazem's effects depend on plasma concentrations of the drug, and that consideration of patient age, size and left ventricular function may allow for effective therapy with a reduced risk of adverse effects.

1429

Prehospital Thrombolysis in Acute Myocardial Infarction

Joachim Schofer, Jochen Büttner, Gabriele Geng, Klaus Gutschmidt, Hans N. Herden, Detlef G. Mathey, Heinz P. Moecke, Peter Polster, Alexander Raftopoulos, Florence H. Sheehan, and Peter Voelz

The benefit and risk of prehospital thrombolysis for acute myocardial infarction were evaluated in a double-blind randomized trial. Patients presenting <4 hours after symptom onset received 2 million units of urokinase as an intravenous bolus either before (group A, $n = 40$) or after (group B, $n = 38$) hospital admission. The mean time to thrombolytic therapy was 85 ± 51 minutes in group A and 137 ± 50 minutes in group B ($p < 0.0005$). Complication rates were low in both groups. Global left ventricular function and regional wall motion and peak creatine kinase were similar in groups A and B. Prehospital thrombolysis using a bolus injection of urokinase has a low risk when performed by a trained physician with a mobile care unit. The saving of 45 minutes in the early stage of an acute infarction through prehospital thrombolysis did not appear to be important for salvage of myocardial function.

1434

Acute Myocardial Infarction and Chest Pain Syndromes After Cocaine Use

Mahesh Amin, Gary Gabelman, Jill Karpel, and Peter Buttrick

Seventy patients hospitalized with chest pain after cocaine use were retrospectively evaluated to define the risk and clinical course of acute myocardial infarction (AMI). AMI developed in 31% and transient myocardial ischemia was seen in an additional 13%. Coronary risk factors did not distinguish those who developed AMI from those who did not. The presenting electrocardiogram was abnormal in 20 of 22 patients who evolved AMI and in 19 of 48 of those who did not. Creatine kinase levels were elevated in 75% of the patients, including 65% of those who did not evolve AMI, but creatine kinase-MB elevations were only observed in the AMI group. The route of cocaine administration did not predict AMI and there was no predilection for a particular coronary vascular bed to be involved. The length of time between drug use and onset of AMI pain was often quite prolonged (median interval, 19 hours in the AMI group vs 1 hour in the non-AMI group). Eight of the AMI patients underwent cardiac catheterization and 4 had significant coronary stenoses. None of the patients died during their hospitalization.

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Comparison of Thallium-201 and Technetium-99m Hexakis 2-Methoxyisobutyl Isonitrile Single-Photon Emission Computed Tomography for Estimating the Extent of Myocardial Ischemia and Infarction in Coronary Artery Disease

Kenneth A. Narahara, Javier Villanueva-Meyer, Craig J. Thompson, Marianne Brizendine, and Ismael Mena

Stress single-photon emission computed tomography (SPECT) using thallium-201 (Tl-201) was compared with technetium-99m hexakis 2-methoxyisobutyl isonitrile (Tc-99m MIBI). An automated method was used to determine normal and hypoperfused left ventricular mass. Determination of total left ventricular mass was similar for both stress/redistribution Tl-201 and stress/rest Tc-99m MIBI images. The mean defect size in the redistribution Tl-201 images was 32 ± 34.7 and 33 ± 38.4 g in the resting Tc-99m MIBI studies (difference not significant). Individual determinations of defect mass were highly correlated ($r = 0.93$). Defect size estimated from the stress Tl-201 images was 52 ± 46.2 g, significantly larger than the exercise Tc-99m MIBI estimates of defect mass (42 ± 39.9 g; $p < 0.05$). Stress Tc-99m MIBI defect sizes defined by visual interpretation or the use of isocount analysis may be smaller than those obtained with stress Tl-201 SPECT.

1445

Recanalization of Chronic Total Coronary Arterial Occlusions by Percutaneous Excimer-Laser and Laser-Assisted Angioplasty

Gerald S. Werner, Arnd Buchwald, Christina Unterberg, Eberhard Voth, Heinrich Kreuzer, and Volker Wiegand

In 39 patients with a chronic coronary occlusion (duration 1 to 12 months), recanalization was attempted by excimer laser angioplasty. A concentric multifiber catheter was used, guided by a central wire. After passing the occlusion by a wire in 27 patients (69%), the laser catheter could be advanced across the occlusion in 25 patients (64%). If the residual stenosis exceeded 50%, laser was followed by additional balloon angioplasty. The residual stenosis after laser was $61 \pm 17\%$ vessel diameter, and after balloon angioplasty $28 \pm 9\%$ ($n = 19$), whereas with stand-alone laser angioplasty it was $38 \pm 5\%$ ($n = 6$). No complications associated with the laser application were observed. Angiographic control after 24 hours showed reocclusion of 2 (8%) recanalized vessels. Laser angioplasty for the treatment of chronic total coronary occlusions proved to be safe and feasible. The primary success was limited by the need for a successful passage of the wire. The limited size of the achieved lumen required additional balloon angioplasty in 76% of cases.

1451

Prevalence and Prognostic Significance of Exercise-Induced Ventricular Arrhythmias After Coronary Artery Bypass Grafting

Sinikka Yli-Mäyry, Heikki V. Huikuri, Ulla R. Korhonen, K.E. Juhani Airaksinen, Markku J. Ikäheimo, Markku K. Linnaluoto, and Juha T. Takkunen

We prospectively followed up 200 patients examined by exercise electrocardiography and cardiac catheterization before and 3 months after coronary artery bypass grafting (CABG). Exercise-induced ventricular arrhythmias occurred more often after (49 of 200 patients, 24.5%) than before (32 of 200 patients, 16.0%) CABG ($p < 0.05$). There were no differences between the patients with and without ventricular arrhythmias in the prevalence of graft patency or the postoperative ejection fraction. Ten cardiac deaths occurred during the mean follow-up time of 61 ± 19 months, 8 of which were witnessed sudden cardiac deaths. All the cardiac deaths occurred in patients who did not have exercise-induced ventricular arrhythmias after CABG. The postoperative ejection fraction was lower in the cardiac death patients ($42 \pm 16\%$) than in the survivors ($58 \pm 10\%$) ($p < 0.01$). No other clinical or angiographic variable predicted the occurrence of cardiac death.

1455

Temporal Relation Between Left Ventricular Dysfunction and Chest Pain in Coronary Artery Disease During Activities of Daily Living

Junichi Taki, Tsunehiro Yasuda, Nagara Tamaki, Scott D. Flamm, Adolph Hutter, Herman K. Gold, Robert Leinbach, and H. William Strauss

This study determined the incidence and temporal sequence of left ventricular (LV) dysfunction, ST-segment depression and chest pain in 43 patients with angiographically documented coronary artery disease. LV function and electrocardiographic changes were monitored for 2.9 ± 1.9 hours using an ambulatory LV monitoring device. In 11 patients, 22 episodes of chest pain, or ST-segment depression, or both, were observed. Eighteen episodes were accompanied by a decrease in ejection fraction (9 patients). In 13 episodes, chest pain was accompanied by a decrease in ejection fraction, whereas ST-segment changes occurred only in 7 episodes. In 12 of the 13 episodes, the decrease in ejection fraction began 56 ± 41 seconds earlier than the onset of chest pain. The average delay from chest pain to ST-segment depression was 99 ± 91 seconds. These data suggest that LV dysfunction manifested by a decrease in ejection fraction precedes angina pectoris or electrocardiographic evidence of myocardial ischemia.

1459

Recanalization of Chronic, Totally Occluded Coronary Arteries by New Angioplasty Systems

Christian W. Hamm, Wolfram Kupper, Karl-Heinz Kuck, Dirk Hofmann, and Walter Bleifeld

We evaluated new angioplasty devices in 154 consecutive patients with chronic total occlusions. The protocol followed a stepwise design: first,

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EMINASE®

ANISTREPLASE 30u

INDICATIONS AND USAGE: EMINASE® ANISTREPLASE is indicated for use in the management of acute myocardial infarction (AMI) in adults, for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see **CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, EMINASE® is contraindicated in the following situations: ■ active internal bleeding ■ history of cerebrovascular accident ■ recent (within 2 months) intracranial or intraspinal surgery or trauma (see **WARNINGS**) ■ intracranial neoplasm, arteriovenous malformation, or aneurysm ■ known bleeding diathesis ■ severe, uncontrolled hypertension. EMINASE® should not be administered to patients having experienced severe allergic reactions to either this product or Streptokinase.

WARNINGS: Bleeding: (See **ADVERSE REACTIONS**) The most common complication associated with EMINASE® therapy is bleeding. The types of bleeding associated with thrombolytic therapy can be divided into two broad categories: 1. Internal bleeding involving the gastrointestinal tract, genitourinary tract, retroperitoneal, ocular, or intracranial sites. 2. Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to the bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of EMINASE® had dissipated, but while heparin therapy was continuing. As fibrin is lysed during EMINASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites). Intramuscular injections and nonessential handling of the patient should be avoided during treatment with EMINASE®. Venipunctures should be performed carefully and only as required. Should an arterial puncture be necessary following administration of EMINASE®, it is preferable to use an upper-extremity vessel that is accessible to manual compression. A pressure dressing should be applied, and the puncture site should be checked frequently for evidence of bleeding. Each patient being considered for therapy with EMINASE® should be carefully evaluated and anticipated benefits should be weighed against potential risks associated with therapy. In the following conditions, the risks of EMINASE® therapy may be increased and should be weighed against the anticipated benefits: ■ recent (within 10 days) major surgery (e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels) ■ cerebrovascular disease ■ recent gastrointestinal or genitourinary bleeding (within 10 days) ■ recent trauma (within 10 days) including cardiopulmonary resuscitation ■ hypertension: systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg ■ high likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation) ■ subacute bacterial endocarditis ■ acute pericarditis ■ hemostatic defects including those secondary to severe hepatic or renal disease ■ pregnancy ■ age >75 years (Use of EMINASE® in patients over 75 years old has not been adequately studied.) ■ diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions ■ septic thrombophlebitis or occluded AV cannula at seriously infected site ■ patients currently receiving oral anticoagulants (e.g., warfarin sodium) ■ any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias: Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when injections of EMINASE® are administered.

Hypotension: Hypotension, sometimes severe, not secondary to bleeding or anaphylaxis, has occasionally been observed soon after intravenous EMINASE® administration. Patients should be monitored closely and, should symptomatic or alarming hypotension occur, appropriate symptomatic treatment should be administered.

PRECAUTIONS: General: Standard management of myocardial infarction should be implemented concomitantly with EMINASE® treatment. Invasive procedures should be minimized (see **WARNINGS**). Anaphylactoid reactions have rarely been reported in patients who received EMINASE®. Accordingly, adequate treatment provisions such as epinephrine should be available for immediate use.

Readministration: Because of the increased likelihood of resistance due to antistreptokinase antibody, EMINASE® may not be as effective if administered more than 5 days after prior EMINASE® or Streptokinase therapy or streptococcal infection, particularly between 5 days and 6 months. Increased antistreptokinase antibody levels between 5 days and 6 months after EMINASE® or Streptokinase administration may also increase the risk of allergic reactions. Repeated administration of EMINASE® within one week of the initial dose has occurred in a small number of patients treated for AMI and non-AMI conditions. The incidence of hematomas/bruising was somewhat greater in those patients who received repeat doses of EMINASE® but otherwise the adverse event profile was similar to those who received one dose.

Laboratory Tests: Intravenous administration of EMINASE® will cause marked decreases in plasminogen and fibrinogen and increases in thrombin time (TT), activated partial thromboplastin time (APTT), and prothrombin time (PT). Results of coagulation tests and/or measures of fibrinolytic activity performed during EMINASE® therapy may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. EMINASE®, when present in blood in pharmacologic concentrations, remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (2000 to 3000 KIU/mL) can, to some extent, mitigate this phenomenon.

Drug Interactions: The interaction of EMINASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as aspirin and dipyridamole) may increase the risk of bleeding if administered prior to EMINASE® therapy.

Use of Anticoagulants: EMINASE® alone or in combination with antiplatelet agents and anticoagulants may cause bleeding complications. Therefore, careful monitoring is advised, especially at arterial puncture sites. In clinical studies, a majority of patients treated received anticoagulant therapy postdosing with EMINASE® during their hospital stay and a minority received heparin pretreatment with EMINASE®. The use of antiplatelet agents increased the incidence of bleeding events similarly in patients treated with EMINASE® or nonthrombolytic therapy. There was no evidence of a synergistic effect of combined EMINASE® and antiplatelet agents on bleeding events. In addition, there was no difference in the incidence of hemorrhagic CVA's in EMINASE® treated patients who did or did not receive aspirin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Studies to determine mutagenicity and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested.

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- Bonnier HJRM, Visser RF, Klopms HC, Hoffman HJML, and the Dutch Invasive Reperfusion Study Group. Comparison of intravenous anisoylated plasminogen streptokinase activator complex and intracoronary streptokinase in acute myocardial infarction. *Am J Cardiol*. 1988;62:25-30.
- Twenty-four-hour reocclusion. Visser RF. Angiographic assessment of patency and reocclusion: preliminary results of the Dutch APSAC reocclusion multicenter study (ARMS). *Clin Cardiol*. 1990;13:V45-V47.

Pregnancy (Category C): Animal reproduction studies have not been conducted with EMINASE®. It is also not known whether EMINASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. EMINASE® should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether EMINASE® is excreted in human milk. Because many drugs are excreted in human milk, the physician should decide whether the patient should discontinue nursing or not receive EMINASE®.

Pediatric Use: Safety and effectiveness of EMINASE® in children have not been established.

ADVERSE REACTIONS: Bleeding: The incidence of bleeding (major or minor) varied widely from study to study and may depend on the use of arterial catheterization and other invasive procedures, patient population, and/or concomitant therapy. The overall incidence of bleeding in patients treated with EMINASE® in clinical trials (n=5275) was 14.6%, with nonpuncture-site bleeding occurring in 10.2%, and puncture-site bleeding occurring in 5.7%, of these patients. Bleeding at the puncture site occurred more frequently in clinical trials in which the patients underwent immediate coronary catheterization (13.3%, n=637) compared with those who did not (3.0%, n=2023). The incidence of presumed intracranial bleeding within 7 days postdosing with EMINASE® was 0.57% (n=5275); 0.34% etiology confirmed hemorrhagic; 0.23% etiology not confirmed) compared to 0.16% (n=1249) after nonthrombolytic therapy. In the ARMS trial the overall incidence of bleeding in patients treated with EMINASE® was 14.8% compared with 3.8% for placebo. The incidence of specific bleeding events was:

Type of Bleeding	EMINASE® (n=500)	Placebo (n=501)
Puncture site	4.6%	<1%
Nonpuncture site hematoma	2.8%	<1%
Hematuria/Genitourinary	2.4%	<1%
Hemoptysis	2.2%	<1%
Gastrointestinal hemorrhage	2.0%	1.4%
Intracranial	1.0%	<1%
Gum/Mouth Hemorrhage	1.0%	0
Epistaxis	<1%	<1%
Anemia	<1%	<1%
Eye Hemorrhage	<1%	<1%
Hemorrhage (unspecified)	<1%	0

In this study there was no difference between EMINASE® and placebo in the incidence of major bleeding events. Should serious bleeding (not controlled by local pressure) occur in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial), any concomitant heparin should be terminated immediately and the administration of protamine to reverse heparinization should be considered. If necessary, the bleeding tendency can be reversed with appropriate replacement therapy. Minor bleeding can be anticipated mainly at invaded or disturbed sites. If such bleeding occurs, local measures should be taken to control the bleeding (see **WARNINGS**).

Cardiovascular: The most frequently reported adverse experiences in EMINASE® clinical trials (n=5275) were arrhythmia/conduction disorders which were reported in 38% of patients treated with EMINASE® and 46% of nonthrombolytic control patients. Hypotension occurred in 10.4% of patients treated with EMINASE® compared to 7.9% for patients who received nonthrombolytic treatment (see **WARNINGS**).

Allergic-type Reactions: Anaphylactic and anaphylactoid reactions have been observed rarely (0.2%) in patients treated with EMINASE® and are similar in incidence to Streptokinase (0.1% anaphylactic shock in one study). These included symptoms such as bronchospasm or angioedema. Other milder or delayed effects such as urticaria, itching, flushing, rashes, and eosinophilia have been occasionally observed. A delayed purpuric rash appearing one to two weeks after treatment has been reported in 0.3% of patients. The rash may also be associated with arthralgia, ankle edema, gastrointestinal symptoms, mild hematuria, and mild proteinuria. This syndrome was self-limiting and without long-term sequelae.

Risk of Viral Transmission: Six batches of EMINASE® (five different batches of Lys-Plasminogen) were used in clinical trials designed specifically to monitor possible hepatitis non-A, non-B transmission. No case of hepatitis was diagnosed in patients receiving EMINASE®. Lys-Plasminogen is derived from human plasma obtained from FDA approved sources and tested for absence of viral contamination, including human immunodeficiency virus type-1 (HIV-1) and hepatitis B surface antigen. The manufacturing process includes a vapor-heat treatment step for inactivation of viruses. The entire manufacturing process has also been validated to yield a cumulative reduction of $\geq 10^{2.1}$ fold HIV-1 infectious particles, i.e., $\geq 10^5$ infectious particles removed by vapor-heat treatment and a cumulative total of $\geq 10^{15}$ infectious particles removed by the various steps in the purification process.

Causal Relationship Unknown: Since the following experiences may also be associated with AMI or other therapy, the causal relationship to EMINASE® administration is unknown. The following adverse experiences were infrequently (<10%) reported in clinical trials: **Body as a Whole**—chills, fever, headache, shock; **Cardiovascular**—cardiac rupture, chest pain, emboli; **Dermatology**—purpura, sweating; **Gastrointestinal**—nausea and/or vomiting; **Hemic and Lymphatic**—thrombocytopenia; **Metabolic and Nutritional**—elevated transaminase levels; **Musculoskeletal**—arthralgia; **Nervous**—agitation, dizziness, paresthesia, tremor, vertigo; **Respiratory**—dyspnea, lung edema.

DOSAGE AND ADMINISTRATION: Administer EMINASE® as soon as possible after the onset of symptoms. The recommended dose is 30 units of EMINASE® administered only by intravenous injection over 2 to 5 minutes into an intravenous line or vein.

Reconstitution: 1. Slowly add 5 mL of Sterile Water for Injection, U.S.P., by directing the stream of fluid against the side of the vial. 2. Gently roll the vial, mixing the dry powder and fluid. Do not shake. Try to minimize foaming. 3. The reconstituted preparation is a colorless to pale yellow transparent solution. Before administration, the product should be visually inspected for particulate matter and discoloration. 4. Withdraw the entire contents of the vial. 5. The reconstituted solution should not be further diluted before administration or added to any infusion fluids. No other medications should be added to the vial or syringe containing EMINASE®. 6. If EMINASE® is not administered within 30 minutes of reconstitution, it should be discarded.

HOW SUPPLIED: EMINASE® is supplied as a sterile, lyophilized powder in 30-unit vials. NDC 57294-030-20.

Storage: Store lyophilized EMINASE® between 2-8°C (36-64°F). Do not use beyond the expiration date printed on the vial.

- In-hospital reocclusion data adapted from Anderson JL, Hackworthy RA, Sorensen SG, et al. Comparison of intravenous anisoylated plasminogen activator complex (APSAC) and streptokinase in acute myocardial infarction: interim report of a randomized, double-blind patency study. *Circulation*. 1989;80(Suppl II):420.
- Forty-eight-hour reocclusion. Jackson D. Summary of early clinical experience with anisoylated plasminogen streptokinase activator complex in the treatment of acute myocardial infarction. *Drugs*. 1987;33 (Suppl 3):104-111.
- Bassand JP, Cassagnes J, Machecourt J, et al. A multicenter trial of intravenous APSAC versus rTPA in acute myocardial infarction: assessment of efficacy and safety. *J Am Coll Cardiol*. 1990;15:64A.

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conventional guidewires and low-profile balloons were used, followed by "balloon-on-the-wire" systems (Probe™, Ace™) or by a shaft-enforced, tip-deflecting catheter (Omniflex™). In 97 patients with occlusions of 2 to 12 weeks' duration, recanalization was achieved in 51 patients (53%) with the conventional approach and in 29 patients with the new devices, raising the success rate to 82%. In 57 occlusions of >12 weeks' duration, the recanalization attempt was successful in 58%, mediated in 16 patients (28%) by the Omniflex catheter. There were no life-threatening complications and only 1 emergency bypass operation was necessary (0.6%). New angioplasty devices are therefore of considerable value in the attempt to improve the results of coronary angioplasty in chronic total occlusions.

1464

Low-Dose Aspirin Versus Anticoagulants for Prevention of Coronary Graft Occlusion

Michael A. J. Weber, Joerg Hasford, Claude Taillens, Alexander Zitzmann, Georg Hahalis, Herbert Seggewiss, Axel F. Langbehn, Dieter Fassbender, Rainer Buchwalsky, Karl Theisen, and Eric Hauf

The prevention of graft occlusion by aspirin (100 mg/day) or heparin followed by phenprocoumon was investigated in a randomized trial in 235 patients after aortocoronary bypass operation. Aspirin treatment was begun 24 hours before, and heparin 6 hours and phenprocoumon 2 days after surgery. The results of the vein graft angiography and the clinical outcome 81 days postoperatively did not differ: 22% of 218 vein graft distal anastomoses in the aspirin group and 20% of 272 in the anticoagulant group were occluded. At least 1 occluded distal anastomosis was present in 38% of 74 patients in the aspirin-treated group and in 39% of 86 patients in the anticoagulant group. Because occlusion rates were equal but high with both drug regimens in these patients with advanced stage of coronary artery disease, a combination of low-dose aspirin and anticoagulation should be investigated to reduce graft occlusion rates further.

SYSTEMIC HYPERTENSION

1469

Arterial Vasodilator Effects of the Dihydropyridine Calcium Antagonist Amlodipine Alone and in Combination with Verapamil in Systemic Hypertension

Wolfgang Kiowski, Paul Erne, Lilly Linder, and Fritz Rolf Bühler

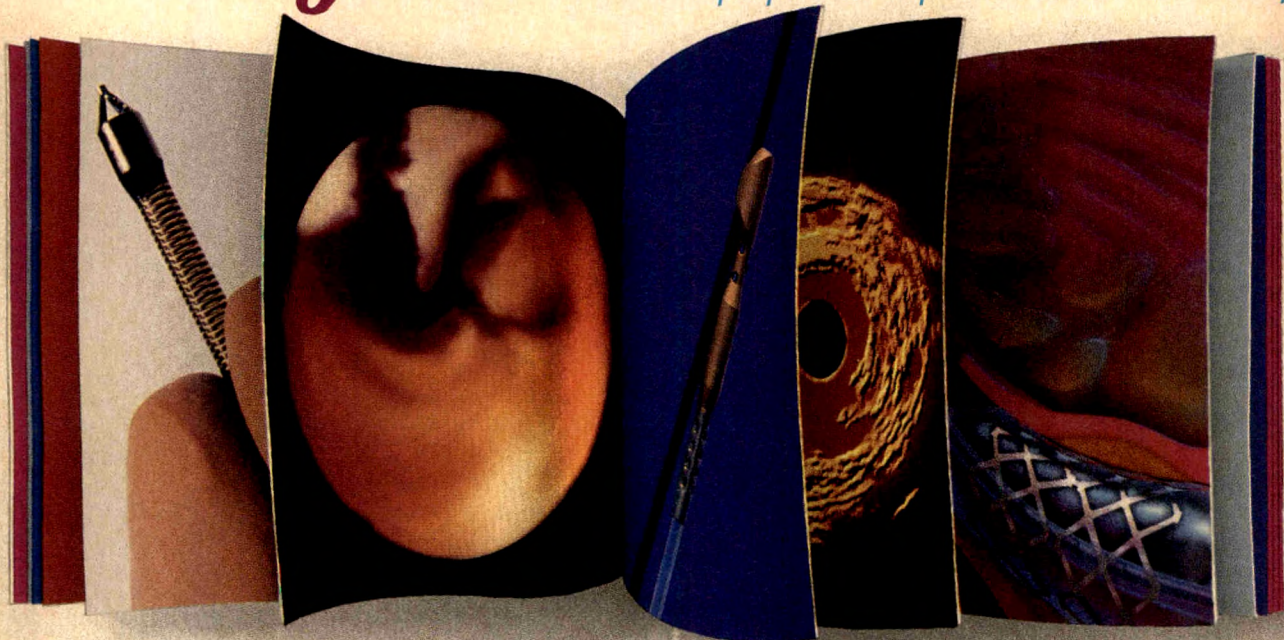
The arterial vasodilator properties of the dihydropyridine calcium antagonist amlodipine were compared with the vascular effects of sodium nitroprusside and with the combined infusion of amlodipine and the nondihydropyridine calcium antagonist verapamil in 8 untreated patients with primary hypertension. Forearm blood flow increased dose dependently during graded brachial artery amlodipine infusions by a maximum of 687%, whereas sodium nitroprusside resulted in an increase of 449%. Combined infusion of amlodipine and verapamil, 44.5 and 40 µg/min/100 ml, respectively, caused an additional significant increase of forearm blood flow above the level seen with amlodipine alone (34.4 vs 23.6 ml/

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min/100 ml). The precise mechanisms behind this finding have yet to be elucidated, and its clinical relevance for the treatment of ischemic heart disease and hypertension needs further study.

CARDIOMYOPATHY

1473

Left Ventricular Filling Impairment in Asymptomatic Chronic Alcoholics

Markku Kupari, Pekka Koskinen, Antti Suokas, and Markku Ventilä

We used M-mode and Doppler echocardiography to study left ventricular size, mass, systolic function and diastolic filling in 32 alcoholics free of heart disease and in 15 healthy control subjects. Compared with control subjects, alcoholics had a higher wall thickness and mass of the left ventricle but there was no difference in end-diastolic diameter index or in fractional shortening. However, alcoholics had a prolonged relaxation time, lower peak velocity and acceleration of the early flow and higher atrial-to-early peak velocity ratio compared with control subjects. These findings suggest that an impairment of early diastolic filling due to delayed relaxation is an early sign of preclinical alcoholic cardiomyopathy.

CONGENITAL HEART DISEASE

1478

Physiologic Peripheral Pulmonic Stenosis in Infancy

Ricardo J. Rodriguez and Thomas W. Riggs

Fourteen premature infants with the clinical diagnosis of peripheral pulmonic stenosis (PPS) and 15 normal full-term neonates were examined by Doppler echocardiography. The PPS group had smaller branch pulmonary artery (PA) diameters: right PA = 0.41 vs 0.50 cm, $p < 0.001$, and left PA = 0.41 vs 0.49 cm, $p < 0.001$. The PPS group also had greater peak velocities in the main PA (76 vs 63 cm/s, $p < 0.05$), right PA (193 vs 118 cm/s, $p < 0.001$) and left PA (187 vs 123 cm/s, $p < 0.001$). It is concluded that patients with PPS have mild underdevelopment of the PA branches, with consequent increased flow velocity and turbulent flow.

1482

Coronary Arteries in Truncus Arteriosus

Maria V. de la Cruz, Raul Cayre, Paolo Angelini, Nicholas Noriega-Ramos, and Stanislaw Sadowinski

The origin and distribution of the coronary arteries were described in 39 autopsy specimens of truncus arteriosus. Specimens were classified according to the number and patterns of truncal cusps. The position of the truncal cusps was defined in relation to intracardiac structures, namely the

Continued on page A29

atrioventricular orifices. Bicuspid truncal valves were observed in 8 cases (21%), tricuspid in 22 cases (56%) and quadricuspid in 9 cases (23%). All tricuspid valves had 2 anterior and 1 posterior cusp. Great variability in the origin of the coronary arteries was observed, with a tendency for the right coronary artery to arise from the anterior right quadrant, and for the left coronary artery to arise from the anterior left quadrant. Such a tendency was observed in 50% of the bicuspid, in 59% of the tricuspid and in 66% of the quadricuspid valves. The anterior surface of the right ventricle was crossed by a right coronary artery in 5 cases. A single coronary artery was observed in 7 cases (18%).

MISCELLANEOUS

1487

Spectrum of Hemodynamic Changes in Cardiac Tamponade

P. Sudhakar Reddy, Edward I. Curtiss, and Barry F. Uretsky

Hemodynamic observations in 77 patients with pericardial effusion indicate that the accumulation of pericardial fluid can be associated with increases in intrapericardial and intraventricular filling pressure, without equalization and without a significant decrease in cardiac output. Rising intrapericardial pressure then appears to equilibrate first with right ventricular filling and then with left ventricular filling pressures associated with a decrease in cardiac output. Exaggeration of the inspiratory decrease in arterial systolic pressure progressively increases with increasing severity in hemodynamic changes. Thus, the hemodynamic changes induced by pericardial effusion are a continuum and cardiac tamponade is not an all-or-none phenomenon.

1492

Transesophageal Echocardiography in Critically Ill Patients

Jae K. Oh, James B. Seward, Bijoy K. Khandheria, Bernard J. Gersh, Christopher G.A. McGregor, William K. Freeman, Lawrence J. Sinak, and A. Jamil Tajik

Transesophageal echocardiography was performed in 51 patients (28 men and 23 women, mean age 63 years) in the intensive care unit and no adverse effects were noted in 49 (96%) of them. The most frequent indication for transesophageal echocardiography was unexplained hemodynamic instability (25 patients, 49%); other indications included evaluation of mitral regurgitation, endocarditis, aortic dissection and potential donor heart. In 30 patients (59%), transesophageal echocardiography identified cardiovascular problems that could not be clearly diagnosed by transthoracic echocardiography. Cardiac surgery was prompted by transesophageal echocardiographic findings in 12 patients (24%), and these findings were confirmed at operation in all cases. Thus, transesophageal echocardiography, a unique extension of the echocardiographic technique, is safe and has an expanding role in the management of critically ill patients suspected of having cardiovascular compromise.

HISTORICAL STUDY

1496

The Developmental Phase of Modern Coronary Artery Surgery

René Gerónimo Favalaro

In this anecdotal history of a landmark era in the development of modern coronary artery surgery, the author reconstructs the Cleveland Clinic cardiovascular team's contributions to myocardial revascularization, paying special homage to the memory of his friend, Dr. Mason Sones.

EDITORIALS

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Atrial Isomerism in the Heterotaxy Syndromes with Asplenia, or Polysplenia, or Normally Formed Spleen: An Erroneous Concept

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Changes in Myocardial Ischemic Threshold During Daily Activities

Shmuel Banai, MD, Mady Moriel, MD, Jesaia Benhorin, MD, Alex Gavish, MD, Shlomo Stern, MD, and Dan Tzivoni, MD

This study assesses the variations in myocardial ischemic threshold (heart rate at the onset of ischemia) during daily activities in patients with ischemic episodes on Holter monitoring. Eighty patients with known coronary artery disease, positive treadmill stress test results and ≥ 2 ischemic episodes during a 24-hour period of Holter monitoring were studied. The lowest and the highest ischemic thresholds were determined for each patient. The mean lowest ischemic threshold was 85 beats/min, and the mean highest ischemic threshold was 109 beats/min. The highest ischemic threshold was identical to ischemic threshold values noted during exercise.

Of the 895 ischemic episodes, 654 (74%) were preceded by a moderate ($>10\%$) increase in heart rate.

The variability of ischemic threshold (difference in percentage between the highest and lowest ischemic thresholds) increased with the number of ischemic episodes (range 2 to 60%). However, in different patients with a similar number of ischemic episodes, different variability was observed. These differences in ischemic thresholds are probably indirect indicators of the vasomotor activity of the coronary arteries in different patients.

(Am J Cardiol 1990;66:1403-1406)

During repeated exercise tests, ST-segment depression develops in the same patient at similar heart rates.^{1,2} The presence of this constant and reproducible myocardial ischemic threshold can be explained by a fixed coronary stenosis, which prevents an increase in coronary blood flow during exertion. During atrial pacing in patients with resting angina, Figueras et al³ found that the ischemic threshold is not constant and that nocturnal ischemia appears at a lower heart rate. Several investigators⁴⁻⁶ demonstrated by Holter monitoring during daily activities that, in the same patient, ischemic episodes developed at significantly lower heart rates than they did during exercise testing. However, the heart rate at which the ST depression developed during repeated ischemic episodes in the same patient was not investigated. In this study we measured variations in the heart rate at the onset of ischemia (ischemic threshold) during different ischemic episodes in 80 patients with coronary artery disease.

METHODS

Patients: A total of 395 patients with coronary artery disease and positive stress test results were screened for this prospective study; 80 patients, who had 1 to 3 days of Holter monitoring during daily activities, with a total monitoring period of 158 days, were found eligible. All patients had coronary artery disease diagnosed on the basis of either a prior myocardial infarction, angiographic evidence of significant coronary artery disease ($>70\%$ narrowing in ≥ 1 major coronary vessel), or typical history of exertional angina; all patients had a positive Bruce protocol treadmill test. Included were patients who had ≥ 2 ischemic episodes on 24-hour ambulatory electrocardiographic monitoring. Excluded from the study were patients with conduction disturbances, or abnormal ST segments on their resting electrocardiogram, if this made the ST-segment analysis inaccurate. Patients with valvular heart disease, unstable angina pectoris or heart failure were also excluded. The mean age of the patients was 62 years (range 36 to 83). There were 69 men and 11 women; 20 had had a previous myocardial infarction ≥ 6 months before the study. Forty-eight of the patients received antiischemic therapy during the monitoring period; 26 received β blockers, 24 received nitrates and 20 received calcium antagonists. None of the patients was receiving digitalis.

Ambulatory electrocardiographic monitoring: The CardioData Prodigy system, combined with a PDP 11/

From the Heiden Department of Cardiology, Bikur Cholim Hospital, and the Hebrew University Hadassah Medical School, Jerusalem, Israel. Manuscript received May 29, 1990; revised manuscript received and accepted July 25, 1990.

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73 computer, was used for the analysis of the magnetic tapes. ACS reel-to-reel 2-channel recorders were used. The electrodes were attached to the V₃ and V₅-like positions.⁷

A myocardial ischemic episode was defined as the transient depression of the ST segment of ≥ 1 mm, horizontal or downsloping, that lasted for ≥ 1 minute and then returned to baseline. The end of episodes was defined as the time of return to 1-mm ST depression.

ST analysis was performed in both channels in a semiautomatic-interactive method. Any deviation detected from the isoelectric PR interval was displayed on the ST trend. Electrocardiographic samples were printed out in real time, 2 minutes before the onset of ST depression, at the onset of ischemia (1 mm of ST depression), at maximal ST depression, at maximal heart rate, and on return to the isoelectric line. Each episode was visually verified both from the ST trend and from the real-time printouts. The ST trend enabled us to detect changes in the ST level and to correlate them with changes in heart rates at intervals of 15 seconds. For each ischemic episode, we recorded the heart rate 2 minutes before the onset of ischemia, at 1-mm ST depression and at its maximal rate during the episode.

The ischemic threshold of each episode was defined as the heart rate at which 1-mm ST depression was observed. If a patient developed 1-mm ST depression dur-

ing different episodes at different heart rates, the lowest heart rate at which ischemia was recorded was regarded as the lowest ischemic threshold, whereas the highest ischemic threshold was defined as the highest heart rate at which 1-mm ST depression was observed during another episode.

The percent variability of ischemic threshold in each patient was defined as the difference between the highest (H) and the lowest (L) heart rate at the onset of 1-mm ST depression divided by the highest (H) ischemic threshold; that is, variability (%) = $(H - L)/H \times 100\%$.

Ischemic episodes were divided into those with an increase ($>10\%$), a decrease ($<10\%$), or no change in heart rate.

Treadmill stress test: This test was performed according to the Bruce protocol within 2 weeks of Holter monitoring and while the patients were maintained on their medications. The stress test was performed on a Quinton Model 3000 with 12-lead electrocardiographic recordings. For each patient we recorded the exercise duration, the heart rate at 1-mm ST depression (ischemic threshold during exercise), and the maximal heart rate achieved.

Statistical analysis: The paired *t* test was used for statistical analysis of the data.

RESULTS

The 80 patients had a total of 895 myocardial ischemic episodes during the 158 days of Holter monitoring. The number of ischemic episodes per patient ranged from 2 to 21 (mean 11.2). The average number of ischemic episodes per day was 5.6. The total duration of ischemia in the whole group was 12,600 minutes (210 hours). The total duration of ischemia per patient ranged from 7 to 803 minutes (mean 130.8 minutes). The duration of ischemia per day varied from 2 to 413 minutes (average 65). The duration of an ischemic episode varied from 1 to 125 minutes (average 12.5). Of the 895 ischemic episodes, 745 (83%) were silent and 150 (17%) were symptomatic.

Ischemic thresholds during daily activities: The lowest ischemic threshold ranged from 48 to 128 beats/min (average 85 ± 17) (Figure 1). The highest ischemic threshold ranged from 79 to 151 beats/min (average 110 ± 19). All patients had ischemic episodes that started at a heart rate above the lowest ischemic threshold.

The average ischemic threshold during treadmill stress testing was 109 ± 17 beats/min (range 80 to 160). The ischemic threshold during exercise tests was statistically significantly higher than the lowest ischemic threshold during daily activity ($p < 0.005$) and was identical to the highest ischemic threshold during daily activities.

In 29 (36%) of the 80 patients, the lowest ischemic threshold was below 80 beats/min. In 65 (81%) of the patients, the lowest ischemic threshold was below 100 beats/min.

Variability of ischemic threshold: The correlation between the number of ischemic episodes per patient and the variability of ischemic threshold is shown in

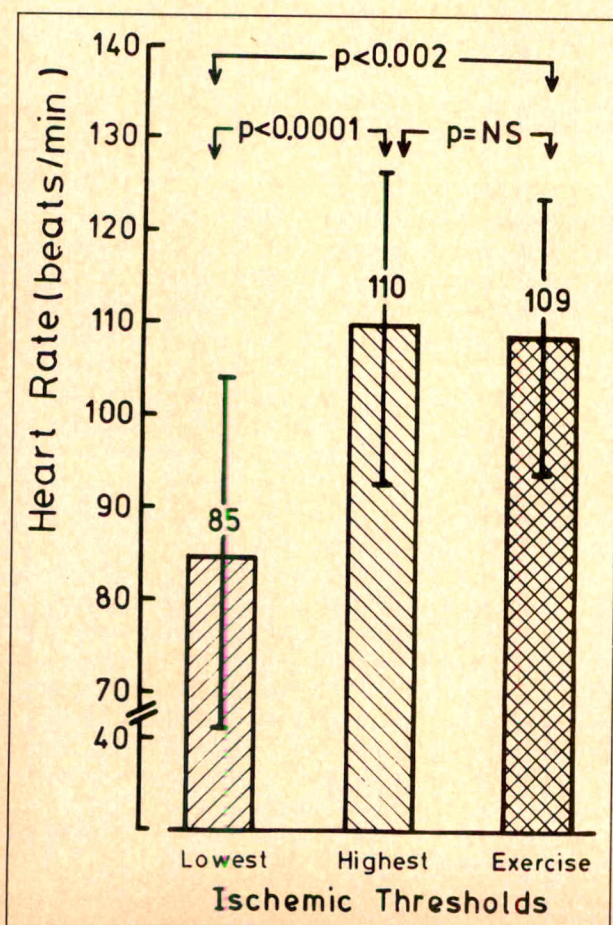


FIGURE 1. Ischemic thresholds during daily activities (lowest and highest) and during exercise. NS = not significant.

Figure 2. Patients with few episodes had less variability than patients with more frequent episodes. Patients with ≤ 10 episodes had an average of 17% variability, compared with 33% in patients with ≥ 10 episodes. However, in different patients with a similar number of episodes, a wide range of variability was observed. Up to 10 to 15 episodes, the variability increased very steeply, with increase in the number of ischemic episodes; beyond 15 episodes, further increase in the number of episodes was associated with only slight increase in variability.

The effect of antiischemic medications on the variability of ischemic threshold could not be assessed in this study, because the patients were not studied before the application of pharmaceutical therapy. The mean variability of patients not receiving medication ($n = 32$) was 21%; for those receiving β blockers ($n = 10$), calcium antagonists ($n = 7$), and nitrates ($n = 5$), the mean variability was 19%, 23% and 18%, respectively. Other patients were receiving combination therapy.

Heart rate and myocardial ischemia: All 80 patients had periods in which the heart rate during daily activity exceeded their lowest ischemic threshold, without developing concomitant ischemic changes.

Heart rate at the onset of ST depression was compared to the heart rate 2 minutes earlier: Of the 895 ischemic episodes detected, 654 (74%) were accompanied by an increase in heart rate of $\geq 10\%$, compared with the heart rate 2 minutes before the onset of ischemia. In 201 (22%) episodes, there was no change in heart rate. In 40 (4%) episodes, a decrease ($<10\%$) in heart rate was noted.

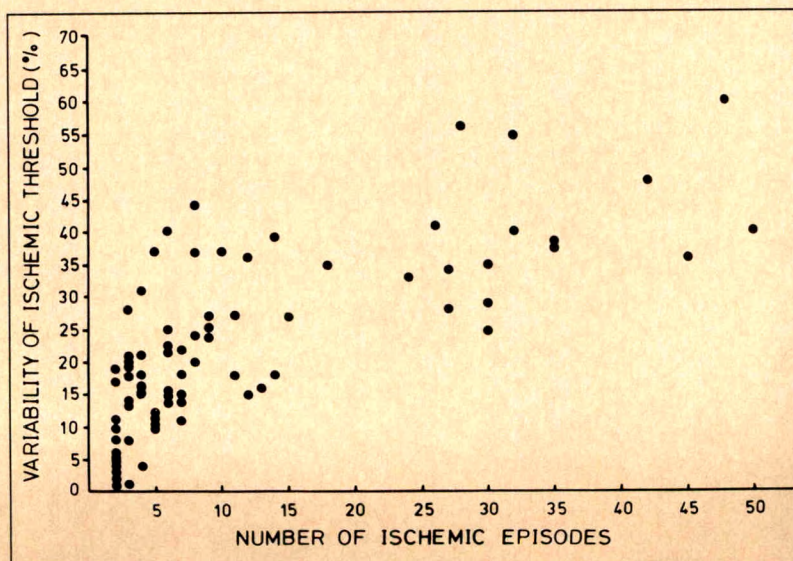
DISCUSSION

We explored the dynamic nature of myocardial ischemia in patients with coronary artery disease in 1976.⁸ Patients were reported to have ischemic changes during routine daily activities with or without physical or emotional stress,⁹⁻¹³ during cigarette smoking,¹⁴ exposure to cold¹⁵ or even during sleep.¹⁶ These ischemic episodes developed at lower heart rates than were noted during

exercise testing, and they were attributed to dynamic changes in coronary tonus. The activity of coronary artery disease varies markedly from patient to patient. We and others found a wide variability in the number and duration of ischemic episodes in different patients, and also in the same patients on different days, weeks or months.^{17,18}

In this study of 80 patients with repeated ischemic episodes, we found that the ischemic threshold during daily activities was not constant. Contrary to previous studies, which measured only the lowest ischemic threshold,^{17,18} in this investigation we measured the heart rate at the onset of all ischemic episodes in each patient. The average lowest ischemic threshold was 85 beats/min, compared with 110 beats/min at the highest ischemic threshold ($p < 0.001$). The mean highest ischemic threshold was identical to the mean ischemic threshold during exercise testing in these patients. The highest ischemic threshold probably represents the condition where coronary blood flow is limited by the fixed stenosis and is therefore constant for the same patient during daily activities, as well as during exercise testing.^{1,2} An ischemic threshold below the highest threshold found by us during daily activities in all patients studied can be attributed to the presence of different degrees of coronary tonus, which reduce coronary blood flow beyond that of the fixed stenosis. Twenty-nine (36%) of the 80 patients developed ischemic changes at heart rates below 80 beats/min and 81% developed changes at heart rates below 100 beats/min. In these patients who developed ischemic changes at a low heart rate, especially if the heart rate was significantly lower than the ischemic threshold during exercise, we assume that the main mechanism of myocardial ischemia is an increase in coronary tonus, in the presence of significant coronary artery disease. It is possible that, in some patients, changes in blood pressure were responsible for the appearance of ST depression at different heart rates; this parameter, however, was not measured in this study. Other unknown factors may also play a role in changing the ischemic threshold.

FIGURE 2. Correlation between number of ischemic episodes and variability of ischemic threshold.



The maximal variability of ischemic threshold was defined by us as the difference between the lowest and highest rates at which ischemic episodes developed in an individual patient. A wide variability in the ischemic threshold was found in our patients: Some had only 2 to 3% variability, whereas, in others, the variability was as high as 60%. The difference in the variability of ischemic threshold may represent different degrees of vasomotor activity in various patients. One may speculate that, in patients with little variability in ischemic thresholds, the vasomotor component is not the major determinant in the development of myocardial ischemia and that their ischemia therefore depends mainly on an increase in oxygen demand.

Patients with marked variability in ischemic threshold may have more dynamic changes in coronary tonus; therefore, it is expected that they will respond to vasodilators. In patients with few ischemic episodes, we found relatively low variability of the ischemic threshold; this may be due to less vasomotor activity. It is possible that, had these patients had more days of monitoring, the maximal variability of ischemic threshold would have been higher. However, even in patients with an identical number of ischemic episodes, extreme differences were found in their variability of ischemic threshold, clearly indicating that this variability is an inherent property of every patient. It seems that the variability of about 40% recorded in patients with >15 ischemic episodes is close to the maximal variability and that adding more episodes will not increase the variability. Brown et al¹⁹ stressed that, in patients with severe coronary artery disease, even slight changes in a cross-sectional area can markedly reduce the coronary flow. This reduction in coronary flow can explain the reduced threshold of ischemia found in our study. One can speculate that the adverse prognosis of patients with frequent ischemic episodes²⁰⁻²³ may be related to increased coronary vasomotor activity among patients with significant coronary artery disease.

The mechanism of myocardial ischemia during daily activities in most patients is a combination of increased coronary tonus and increased oxygen demand; as in most of our patients, although the ischemic threshold was lower than that during exercise testing, a moderate increase in heart rate preceded ischemia in 74% of the episodes. All 80 patients had periods in which the heart rate during daily activities was faster than that at the lowest ischemic threshold, without developing ischemic changes. We assume that during these periods of increase in oxygen demand, the coronary tonus was reduced; therefore, they did not develop ischemia.

Our findings of up to 40% variability of ischemic threshold in patients with stable angina pectoris may not represent the variability in other groups of patients with unstable angina, variant angina, or postinfarction angina. Further studies are required to assess the vari-

ability of myocardial ischemic threshold in patients with each of these entities of coronary artery disease.

Acknowledgment: We are indebted to Noa Dody and Vita Linde for devoted technical help and to Hanna Sebag for secretarial assistance.

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Changes in Standard Electrocardiographic ST-Segment Elevation Predictive of Successful Reperfusion in Acute Myocardial Infarction

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The ability of the electrocardiographic ST segment to predict successful reperfusion after thrombolytic therapy remains controversial. To evaluate whether angiographically determined reperfusion could be predicted from changes in ST-segment elevation, the sum of ST-segment elevation in affected leads of the electrocardiogram was compared before and after thrombolytic therapy in 53 patients with acute myocardial infarction (AMI). Reperfusion status of the infarct-related artery was determined angiographically <8 hours from onset of symptoms. According to the Thrombolysis in Myocardial Infarction trial (TIMI) criteria, 33 patients had successful reperfusion (TIMI grade 2 to 3 flow) after thrombolytic therapy and 20 patients did not (TIMI grade 0 to 1 flow). Logistic multiple regression analysis showed that the proportional value for the shift in the sum of ST elevation, termed the "% ST change," was more strongly associated with reperfusion than the absolute measured difference in millimeters (chi-square = 11.34 vs 9.22). The entire spectra of sensitivities and specificities were determined to identify a level of the percent ST change with simultaneous high sensitivity and specificity. A 20% decrease in ST elevation provided such a level (88% sensitivity, 80% specificity). The positive and negative predictive values of a 20% decrease in ST elevation were 88 and 80%, respectively. These results suggest that a decrease of only 20% in the sum of ST elevation in the standard electrocardiogram after thrombolytic therapy is a useful noninvasive predictor of reperfusion status in patients with evolving AMI.

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Early and sustained myocardial reperfusion after intravenous thrombolytic therapy in patients with acute myocardial infarction (AMI) has led to a reduction in mortality.¹ The only direct diagnostic method to confirm myocardial reperfusion via the infarct-related coronary artery is emergency cardiac catheterization, which despite inherent disadvantages remains the standard for determining reperfusion status. Noninvasive methods are therefore needed to determine the reperfusion status and guide the clinical decision regarding cardiac catheterization. Patients with no reperfusion could be identified and receive a rescue intervention aimed at AMI reperfusion.

The standard 12-lead electrocardiogram is the only diagnostic test immediately available to the physician when making the clinical diagnosis of AMI. Detection of AMI reperfusion from quantitative changes in the electrocardiogram would provide an ideal noninvasive method. It has been established that the natural history of ST-segment resolution during AMI is altered by myocardial reperfusion.²⁻⁸ Despite these findings controversy still exists about the clinical usefulness of the ST segment as a marker of reperfusion.⁹⁻¹² This prospective study was designed to identify the quantitative serial changes in ST-segment elevation during attempted thrombolysis that best predicts successful and unsuccessful AMI reperfusion.

METHODS

Patient group: During an 8-month period, patients admitted to the Duke University interventional cardiac catheterization laboratory for evaluation of AMI were considered for the study. A total of 53 patients met the following inclusion criteria: (1) chest pain ≥ 30 minutes' duration unresponsive to sublingual nitroglycerin therapy, (2) no history of AMI or angioplasty within 48 hours, (3) no left bundle branch block on the electrocardiogram, (4) electrocardiographic evidence of epicardial injury defined as ≥ 0.1 mV of ST-segment elevation in ≥ 2 contiguous leads, and (5) cardiac catheterization performed within 8 hours of symptom onset. Most of the study patients had initially presented to a referring community hospital where thrombolytic therapy had been initiated. The patients were then transported by ambulance or helicopter to Duke University Medical Center and immediately taken to the interventional cardiac catheterization laboratory.

TABLE I Patient Characteristics

	Reperfused Group 1 (n = 33)	Nonreperfused Group 2 (n = 20)
Age (range)	59 (35–79)	58 (32–79)
Infarct coronary artery		
Left anterior descending	15 (46%)	12 (60%)
Right	13 (39%)	6 (30%)
Left circumflex	5 (15%)	2 (10%)
Thrombolytic agent		
Tissue plasminogen activator	12 (37%)	8 (40%)
Streptokinase	10 (30%)	3 (15%)
Urokinase	6 (18%)	3 (15%)
Tissue plasminogen activator + urokinase	5 (15%)	1 (5%)
None	0 (0%)	5 (25%)
Time to ST ₁	66 (27–112)	56 (38–111)
Time to ST ₂	275 (238–335)	271 (210–308)
Time to ST ₁ to ST ₂	209 (77–371)	168 (58–365)

Time = minutes from symptom onset. ST₁ and ST₂ = admission and preangiographic electrocardiographic ST-segment measurements.

Thrombolytic therapy: The pharmacologic thrombolytic therapy differed among the patients according to the different treatment protocols at the referring hospitals. The following thrombolytic agents were administered: tissue plasminogen activator in 20, streptokinase in 13, urokinase in 9, and a combination of urokinase and tissue plasminogen activator in 6; no thrombolytic therapy was given to 5 patients.

Acute cardiac catheterization: The infarct-related artery was identified and visualized in multiple projections by serial contrast injections. The angiograms were recorded and stored for later interpretation by 2 experienced observers who were not involved in the acute intervention procedures. Reperfusion of the infarct-related coronary artery was determined according to the classification of the Thrombolysis in Myocardial Infarction trial (TIMI).¹³ The initial injection was used for analysis in this study because it represented the effect of the thrombolytic agent without the influence of repeated contrast injections.

Electrocardiographic analysis: The electrocardiograms were obtained by 2 investigators who were not involved in the acute management of the patients. When multiple "admission" recordings were obtained before initiation of thrombolytic therapy the electrocardiogram showing the maximal sum of ST-segment deviation was used in the subsequent analysis (ST₁). A "pre-angiographic" electrocardiogram was obtained immediately (<5 minutes in all patients) before angiographic determination of the reperfusion status of the infarct artery (ST₂). ST-segment elevation was measured to the nearest 0.05 mV at the J point in 11 of the 12 electrocardiographic leads (aVR excluded). All electrocardiograms were read by 3 investigators who were blinded from the clinical information.

Data analysis: Patients with TIMI grades 2 or 3 flow were considered to have achieved reperfusion (group 1) and patients with grades 0 or 1 flow were considered to have not achieved reperfusion via the infarct-related artery (group 2). The sum of the ST-seg-

TABLE II Sum of Electrocardiographic ST-Segment Elevation on Admission and Before Coronary Angiography

	Reperfused Group 1 (n = 33)	Nonreperfused Group 2 (n = 20)
Admission electrocardiogram		
ST ₁ in mm	8 (5–10)	11 (6–17)
Preangiographic electrocardiogram		
ST ₂ in mm	3 (1–6)	11 (8–19)
p Value	0.00003	0.31

ment elevation was calculated on the admission electrocardiogram (ST₁) and on the preangiographic electrocardiogram (ST₂). The "ST difference" (ST₂ – ST₁) was compared in the 2 groups. Also, to provide a quantitative expression of the difference between ST₁ and ST₂ that corrected for the baseline value (ST₁) the following formula was applied: (ST₂ – ST₁) × 100/ST₁, and will subsequently be referred to as the "% ST change." Thus, complete resolution (↓) of ST elevation between ST₁ and ST₂ resulted in a % ST change of 100%↓. Unchanged ST elevation resulted in a % ST change of 0%. A twofold increase (↑) resulted in a % ST change of 100%↑.

Statistical analysis: Discrete variables are presented as percentages and continuous variables as medians (interquartile range). Logistic regression analysis was used to examine individually the strength of the association between the outcome variable (reperfusion) and the ST-segment changes. The method most strongly associated with reperfusion was used to calculate curves for sensitivity and specificity to determine the quantity of ST-segment resolution that best discriminated between patients who did or did not have successful reperfusion. Comparisons within groups were made using the Wilcoxon 1 sample rank sum test.

RESULTS

Of the 53 patients evaluated, 33 patients had documented successful reperfusion after thrombolytic therapy. The remaining 20 patients did not have successful reperfusion either despite or without having received thrombolytic therapy. Table I lists the patients' characteristics in the 2 groups. There were no substantial differences in the distribution of infarct-related arteries or the types of thrombolytic agents administered. The times from the onset of symptoms until electrocardiographic ST-segment measurements (ST₁ and ST₂) were nearly identical in the 2 groups. The sums of ST elevations in the 53 patients are listed in Table II. There was a statistically significant reduction in the sum of ST elevation between ST₁ and ST₂ in patients who had reperfusion before acute cardiac catheterization.

To determine whether the ST difference or the percent ST change in the sum of ST elevation was most closely associated with reperfusion via the infarct-related coronary artery, a logistic regression analysis was performed. The % ST change (Figure 1b) more clearly separated the patients with successful and unsuccessful AMI reperfusion than did the ST difference (Figure

1a). The association with reperfusion was stronger using the % ST change (chi-square = 11.34, $p = 0.0008$) compared to the ST difference (chi-square = 9.22, $p = 0.003$). Thus, for subsequent analysis the % ST change was used.

Figure 2 depicts the spectra of sensitivities and specificities attained by the various levels of % ST changes. The sensitivity and specificity curves intersect at a level of approximately $\geq 20\% \downarrow$ from the admission of ST elevation. At this level the % ST change provides a diagnostic test with both high sensitivity (88%) and specificity (80%). As depicted in the figure, an increase in sensitivity or specificity to $>90\%$ can only be obtained at the expense of reducing the specificity or the sensitivity to 60 and 58%, respectively. At the $20\% \downarrow$ level in % ST change the electrocardiogram provides a diagnostic test with a positive predictive value of 88%. Thus, using this level would correctly identify 88% of patients as having achieved reperfusion after thrombolytic therapy, and only 12% without reperfusion being falsely considered as reperfused. The negative predictive value at this level is 80%, reflecting the percentage of patients with failure to achieve reperfusion who would be correctly

identified, and considered for further AMI reperfusion therapy.

Figure 3 presents examples of electrocardiographic recordings before and after thrombolytic therapy in study patients with infarcts in inferior and anterior locations. Despite angiographically documented reperfusion, only partial ST resolution occurred.

DISCUSSION

The present study documents the usefulness of the standard electrocardiographic ST segment as a noninvasive predictor of coronary artery reperfusion after intravenous thrombolytic therapy for AMI. Use of the % ST change as a diagnostic test provides a method with sufficient specificity and sensitivity to help identify nonreperfused patients who could benefit from emergent cardiac catheterization with adjunctive intracoronary pharmacologic or mechanical treatments to restore infarct artery patency. The results of this study indicate the importance of using each patient as his own control, to compare any change in ST-segment elevation to the baseline value rather than observing a change in absolute numbers of millimeters. The study revealed that a

FIGURE 1. Cumulative frequency curves showing the percentages of patients identified in groups 1 and 2 at different levels of ST segment changes. *a*, using the ST difference ($ST_2 - ST_1$); *b*, using the % ST change (see Methods).

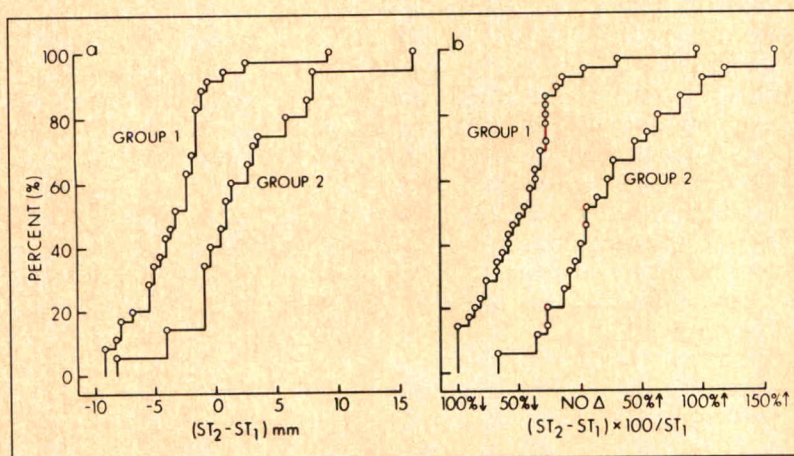
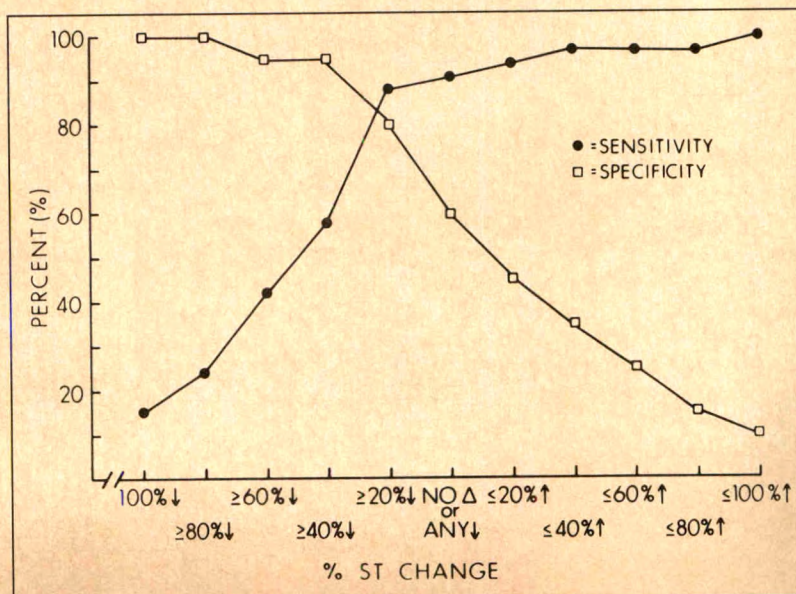


FIGURE 2. Spectra of sensitivities and specificities per % ST change in ST-segment elevation for identifying patients with myocardial reperfusion via a patent coronary artery. Values of sensitivity and specificity are given for each level of % ST change. For example, a % ST change of $\geq 20\% \downarrow$ had a sensitivity of 88% and a specificity of 80% for identifying patients with reperfusion.



% ST change of $\geq 20\%$ provided a method that is both specific and sensitive. Several previous studies have suggested that the extent and magnitude of ST-segment deviation observed on the standard electrocardiogram during acute coronary occlusion reflects the ischemic burden on the left ventricle. The acute ST-segment deviation has been shown to predict final AMI size in patients receiving no reperfusion therapy¹⁴⁻¹⁶ and the extent of new wall motion abnormality during angioplasty balloon inflation.¹⁷ Changes in ST-segment deviation might therefore reflect variations in the extent of myocardial ischemia.

Although previous studies have found a rapid resolution in ST-segment deviation associated with successful reperfusion,³⁻⁸ the usefulness of these changes in identifying infarct artery patency status remains controversial. A study of 386 patients by Califf et al¹² found that changes in the ST-segment deviation was a stronger predictor of coronary artery patency than variations in chest pain or arrhythmias. A method for identifying infarct artery patency, which yielded both high sensitivity and specificity, could not be proposed from this study. However, the recording of changes in ST segment were only graded qualitatively (resolved, improved or unchanged). Kircher et al¹⁸ found that ST-segment improvement occurred in only 33% of patients treated with thrombolytic therapy and was associated with an 88% probability of reperfusion. Richardson et al,¹¹ using abrupt electrocardiographic changes as an indicator of patency, found that absence of such changes was a poor predictor of an occluded artery. However, abrupt ST-T changes were defined as ≥ 2 mm resolution in ST elevation or depression and ≥ 3 mm reduction in T-wave height without considering the patients' baseline ST-T changes. Also, this study might have included patients

with silent coronary reocclusion since patency was determined up to 10 days after thrombolysis. Krucoff et al¹⁰ found that achievement of a stable ST segment within 100 minutes after completed streptokinase infusion was 89% sensitive and 82% specific for the detection of reperfusion. However, their method was based on 3-lead Holter monitoring which is not routinely available and detection of steady state requires continued ST-segment measurement during a 24- to 48-hour period. Hogg and co-workers,⁹ observing the maximally deviated lead on the standard 12-lead electrocardiogram, found that a 50% reduction in ST elevation was 67% specific and 93% sensitive for infarct artery patency. However, the test population was small ($n = 17$) with only 3 patients having occluded coronary arteries.

Part of the controversy on the ST segment as an indicator of reperfusion might result from methodologic differences between the studies, and the fact that the number of electrocardiographic leads considered in these studies rarely exceeded 3. It has been shown that quantification of the ST elevation in all affected electrocardiographic leads during acute coronary occlusion correlates with both development of new wall motion abnormalities and the final AMI size in nonreperfused patients.¹⁵⁻¹⁷ Thus, considering all affected electrocardiographic leads should theoretically prove superior to single lead analysis. For this purpose, continuous ST-segment monitoring has recently become clinically available through microprocessor-driven real-time 12-lead electrocardiographs.¹⁹

By describing the entire spectra of sensitivities and specificities, the present study demonstrates how the electrocardiogram as a noninvasive marker of reperfusion is vulnerable to the arbitrary or qualitative "cut-off" values of ST-segment shift used in previous stud-

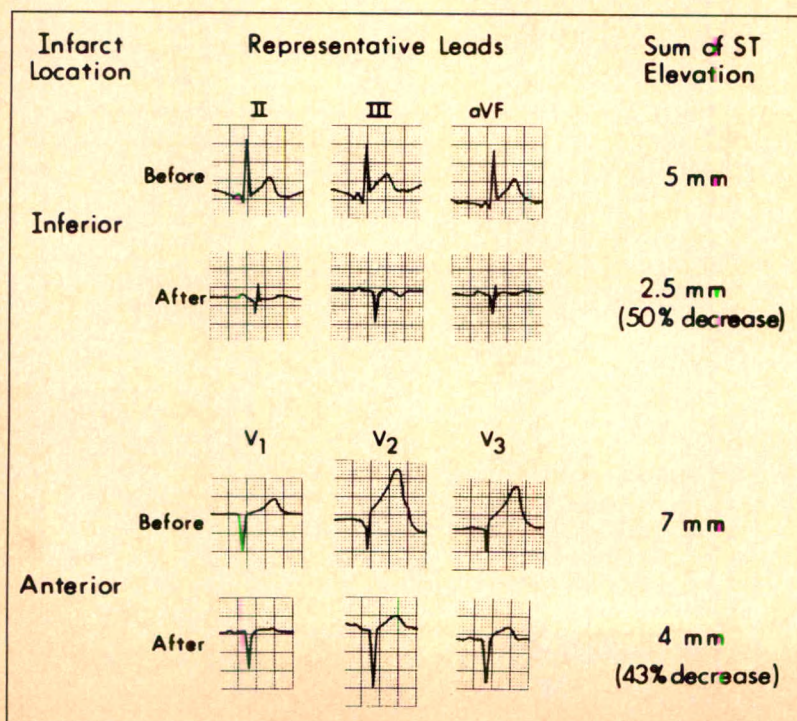


FIGURE 3. Example of study patients with inferior (top) and anterior (below) infarct location. The leads with the maximal ST-segment change (II, III and aVF for inferior and V₁, V₂ and V₃ for anterior) are presented from before thrombolytic therapy (before) and at the time of initial coronary angiography (after). The measurements at right refer to the sum of ST elevation in those leads.

ies.^{9,11,12,18} Clinical use of the results of the present study might be expected to produce the following outcome. Of 100 patients treated with a thrombolytic agent associated with an 80% reperfusion rate, 26 patients would be recommended for emergent cardiac catheterization, based on the predictive values found in the present study. Of the 26 patients, 16 nonreperfused patients would be correctly identified, but the angiography would reveal that reperfusion had already occurred in the other 10. Only 4 patients without reperfusion would be falsely considered as reperfused, and thus miss the opportunity of a rescue procedure, whereas 70 patients would have a correct noninvasive diagnosis of reperfusion.

Other investigators have evaluated enzymatic methods as markers of reperfusion, particularly creatine kinase, its isoenzymes and isoforms, but a clinically useful algorithm based on these serum markers has not yet been developed.²⁰⁻²² The current limitations of these methods include lack of rapid analytic techniques and standardized techniques between laboratories. Unlike the standard electrocardiogram, the analytic kits for determining cardiac enzymes varies between institutions, and therefore "methods" for detection of reperfusion established in one laboratory may not agree with others. However, it is possible that combinations of electrocardiographic and serum markers of reperfusion may prove superior to either method used alone.

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APPENDIX

Method for calculating sensitivity, specificity and predictive values of the ST segment for identification of patients with reperfusion of the infarct-related artery.

SENSITIVITY = number of patients with reperfusion and percent ST change criteria present/number of patients with reperfusion.

SPECIFICITY = number of patients without reperfusion and without percent ST change criteria present/number of patients without reperfusion.

POSITIVE PREDICTIVE VALUE = number of patients with reperfusion and percent ST change criteria present/number of patients with percent ST change criteria present.

NEGATIVE PREDICTIVE VALUE = number of patients without reperfusion and without percent ST change criteria present/number of patients without percent ST change criteria present.

Effect of Heparin on Coronary Arterial Patency After Thrombolysis with Tissue Plasminogen Activator in Acute Myocardial Infarction

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Infarct artery patency rates at 90 minutes after coronary thrombolysis using recombinant tissue-type plasminogen activator (rt-PA) with and without concurrent heparin anticoagulation have been shown to be comparable. The contribution of heparin to efficacy and safety after thrombolysis with rt-PA is unknown. In this pilot study, 84 patients were treated within 6 hours of onset of acute myocardial infarction (mean of 2.7 hours) with the standard dose of 100 mg of rt-PA over 3 hours. Forty-two patients were randomized to receive additionally immediate intravenous heparin anticoagulation (5,000 U of intravenous bolus followed by 1,000 U/hour titrated to a partial thromboplastin time of 1.5 to 2.0 times control) while 42 patients received rt-PA alone. Coronary angiography performed on day 3 (48 to 72 hours, mean 57) after rt-PA therapy revealed infarct artery patency rates of 71 and 43% in anticoagulated and control patients, respectively ($p = 0.015$). Recurrent ischemia or infarction, or both, occurred in 3 (7.1%) anticoagulated patients and 5 (11.9%) control patients (difference not significant). Mild, moderate and severe bleeding occurred in 52, 10 and 2% of the group receiving anticoagulation, respectively, and 34, 2 and 0% of patients in the control group, respectively ($p = 0.006$).

These data indicate that after rt-PA therapy of acute myocardial infarction, heparin therapy is associated with substantially higher coronary patency rates 3 days after thrombolysis but is accompanied by an increased incidence of minor bleeding complications.

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Anticoagulation has long played a role in the prevention and management of thromboembolic complications of acute myocardial infarction.¹⁻³ The role of antithrombotic therapy after pharmacologic thrombolysis in myocardial infarction is incompletely characterized. To date, in most trials, heparin anticoagulation has been routinely, but empirically, added to thrombolytic therapy of acute myocardial infarction in an effort to maximize thrombolytic efficacy and minimize the risk of thrombotic reocclusion.³⁻⁵ The timing and dose of heparin have varied widely but it has been added to recombinant tissue-type plasminogen activator (rt-PA), streptokinase, anistreplase, urokinase and prourokinase (single chain urokinase-type plasminogen activator or scu-PA) in the setting of acute myocardial infarction.⁶⁻¹³

The contribution of heparin therapy to early coronary thrombolytic efficacy with rt-PA has been prospectively evaluated in a trial by the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study group of 134 patients.¹⁴ Infarct coronary arterial status was determined angiographically after 90 minutes in patients randomized either to rt-PA therapy alone or to rt-PA plus heparin (10,000 U intravenous bolus) delivered at the start of the rt-PA infusion. Coronary patency rates at 90 minutes were 79% in both groups. Thus, because anticoagulation did not play a significant role in achieving reperfusion, any expected effect of heparin would be observed after thrombolysis. However, in this trial all patients received heparin during and after angiography at 90 minutes, so the effects of anticoagulation on reocclusion, recurrent clinical events and bleeding after thrombolytic therapy could not be assessed. This pilot study assesses the role of heparin therapy after thrombolytic therapy of acute myocardial infarction with rt-PA.

METHODS

Patients: Patients experiencing acute myocardial infarction and presenting to one of the participating investigation sites were eligible for inclusion in this study. Myocardial infarction was defined as (1) chest pain of ≥ 30 minutes' duration and (clinically) consistent with coronary ischemia; (2) ST-segment elevation on electrocardiogram of ≥ 0.1 mV in at least 1 of 3 locations (anterior [≥ 2 of the 6 precordial leads V_1 - V_6]; inferior [≥ 2 of 3 inferior leads (II, III, aVF)]; or lateral [leads I and aVL]); and (3) onset of index symptoms must have oc-

curred within 6 hours of the time of entry into the study protocol. Men and postmenopausal women were eligible for inclusion. Standard exclusion criteria for thrombolytic therapy in acute myocardial infarction were used.^{6,7,9,10} Recent therapy with aspirin or other platelet inhibitory agent was not an exclusion criterion.

Protocol for study drug administration: After obtaining informed consent, all eligible patients received lidocaine therapy before and during thrombolytic therapy. Patients received 100 mg of alteplase, recombinant brand of t-PA (Activase®), provided by Genentech, Inc. of South San Francisco. Administration was initiated with a bolus of 6 mg given intravenously over 2 minutes followed by 54 mg infused over the first hour. The remaining 40 mg was delivered at 20 mg/hour during the second and third hour of the infusion.

Each center was provided with a treatment allocation sequence based on a randomly generated list of numbers. In patients randomized to receive anticoagulation, unblinded heparin therapy was initiated within the first hour of the rt-PA infusion with an intravenous bolus of 5,000 U followed with an infusion of 1,000 U/hour titrated to maintain the partial thromboplastin time at 1.5 to 2.0 times control value. The first partial thromboplastin time was determined 12 hours after initiation of the heparin infusion. Heparin was continued until the time of coronary angiography.

Patients entered into either arm of the study were precluded from receiving aspirin or dipyridamole during the study period.

Study end points: Because heparin has no angiographically observable effect during thrombolytic reperfusion,¹⁴ the purpose of this study was to evaluate the role of heparin after rt-PA in the maintenance of infarct artery patency early during the course of acute myocardial infarction. The primary end point was coronary arterial patency rate documented on angiography performed on day 3 (48 to 72 hours) after therapy. Since patency rates at 90 minutes are similar in the presence or absence of heparin, any observed angiographic difference could be attributed to heparin effect. In addition, clinical reocclusion was defined by recurrence of (1) cardiac-type chest pain similar to that which occurred with the index myocardial infarction lasting ≥ 20 minutes, unrelieved by nitroglycerin; (2) electrocardiographic changes consistent with ischemia (described previously) in the same distribution as the index myocardial infarction; or (3) deterioration in clinical condition consistent with reinfarction. Electrical and mechanical complications were not considered study end points unless associated with reinfarction. Treatment of recurrent coronary ischemia and complications of infarction were at the discretion of the investigators.

The secondary end point of the study was evaluation of the contribution of heparin to the incidences of bleeding after thrombolytic therapy. All bleeding occurrences were noted, with recording of date, site and an estimate of severity according to the following classification: (1) minor—of no clinical consequence, not requiring transfusion, blood loss of <250 ml; (2) moderate—250 to 500 ml observed blood loss; (3) severe— >500 ml blood

TABLE I Patient Population

	Group A— Anticoagulation	Group B— Control
Therapy	rt-PA plus heparin	rt-PA alone
No. of patients	42	42
Men (%)	79	83
Age (mean years)	59.4	56.6
Weight (mean kg)	80.3	81.4
Time from onset of chest pain to rt-PA therapy (mean hours)	2.6	2.8
Infarct location (%)		
Anterior (\pm lateral)	45	50
Inferior	55	50
Time from rt-PA therapy to angiography (mean hours)	59.6	55.1

p = not significant for all variables.
rt-PA = recombinant tissue-type plasminogen activator.

loss requiring transfusion for augmentation of hematocrit; and (4) life-threatening—evidence of any intracranial bleeding, or gastrointestinal or other internal bleeding causing hypotension. In cases in which >1 bleeding event was noted, the most severe instance was used for statistical analysis.

Protocol for angiographic studies: Coronary angiography was planned for all study patients 48 to 72 hours after treatment with thrombolytic therapy. Institutional protocol was followed during the angiographic procedure. Status of the infarct artery was determined during consensus reading by 2 senior angiographers according to Thrombolysis in Myocardial Infarction (TIMI) flow grade criteria.¹⁵ Infarct arteries with TIMI flow grades 0 and 1 were further classified as "occluded" and flow grades 2 and 3 as "patent."

Statistical analysis: The purpose of this study was to estimate the magnitude of the heparin effect on the primary and secondary end points being evaluated (i.e., coronary arterial patency and bleeding complications, respectively). An initial total sample size of 100 patients was projected for this pilot effort. Fisher's exact test was used to determine significance of dichotomous variables and an exact test was used for ordered categorical variables.¹⁶ All p values reported are 2-sided.

RESULTS

From October 1987 to August 1988, a total of 95 patients were randomized in this pilot clinical trial at 4 participating centers. For reasons described later, 11 patients did not undergo protocol angiography and are not included in the data analysis. Of 84 evaluable patients, 42 received rt-PA plus immediate heparin therapy (group A—anticoagulation) and 42 received rt-PA alone (group B—control). The baseline demographic and clinical characteristics of the 2 groups are listed in Table I.

Angiography was performed a mean of 59.6 hours after rt-PA treatment in the anticoagulation group and 55.1 hours after rt-PA in the control group. Infarct artery assessment revealed a significant difference in patency between the 2 groups. A TIMI flow grade of 2 or 3 was seen in 30 of 42 patients (71%) in the heparin group and in 18 of 42 patients (43%) in the control

TABLE II Sites of Bleeding Complications

	Anticoagulation	Control
Minor bleeding		
Venipuncture site	10	6
Ecchymosis	8	4
Upper extremity hematoma	4	3
Gingival bleeding	3	1
Microscopic hematuria	1	2
Occult gastrointestinal bleeding	1	2
Ear	1	0
Femoral hematoma	1	0
Skin due to trauma	1	0
Epistaxis	0	1
Tongue	0	1
Moderate bleeding		
Deltoid hematoma	1	0
Foot due to trauma	1	0
Hip hematoma	1	0
Knee effusion	1	0
Vaginal	0	1
Severe bleeding		
Oropharyngeal due to endotracheal trauma	1	0

Note: More than 1 bleeding complication occurred in some patients.

group ($p = 0.015$). One of the patients demonstrating clinical reocclusion in the control group died before angiography because of infarct extension and was considered to have an occluded infarct artery (grade 0). The results of angiography are illustrated in Figure 1.

Three patients (7.1%) in the group receiving heparin and 5 patients (11.9%) in the control group demonstrated protocol-defined clinical evidence of reocclusion during the study period. This difference did not approach statistical significance ($p = 0.71$). The mean time of reocclusion was similar in the 2 groups, 27.5 hours (range 5.3 to 71.0) in the heparin group and 28.4 hours (range 3.3 to 62.9) in the control group.

Bleeding occurred in 64% of patients in the group receiving heparin (minor bleeding in 52%, moderate in

10% and severe in 2%) and in 36% of patients in the control group (minor in 33% and moderate in 2%) ($p = 0.006$). Sites of bleeding are listed in Table II.

Eleven patients were excluded from the final analysis for the following reasons: Four patients died because of complications of the index myocardial infarction (not related to reinfarction) before undergoing angiography (2 from group A [sudden cardiac death in 1 and progressive cardiogenic shock in the other] and 2 from group B [sudden cardiac death in both]); in 2 patients, cardiac enzymes failed to confirm presence of myocardial infarction (1 each from groups A and B); 2 patients randomized to the control group received heparin owing to clinical considerations (1 for angiographically apparent intracoronary thrombus during angioplasty for failed thrombolysis and 1 as empiric therapy of recurrent chest pain not meeting above protocol criteria for reocclusion); and 1 patient in the control group was removed from the study because of physician preference (patient considered to be at "high risk" for continuation in the study; patient had neither bleeding complications nor recurrent ischemic complications). In addition, since the purpose of the study was to evaluate the postthrombolysis course, 2 patients experiencing complications during the rt-PA infusion were excluded from the final analysis: 1 patient experienced an autopsy-proven thromboembolic cerebrovascular accident during rt-PA therapy and 1 patient with an undisclosed history of recent motor vehicle trauma died during rt-PA therapy because of massive internal hemorrhage.

DISCUSSION

Patent artery hypothesis: The potential importance of a patent infarct artery during the recovery phase of acute myocardial infarction has recently been reviewed¹⁷ and is the subject of ongoing clinical trials. Reduction in mortality and improved prognosis have been observed even when infarct artery reperfusion is presumed to have occurred as late as 24 hours after myo-

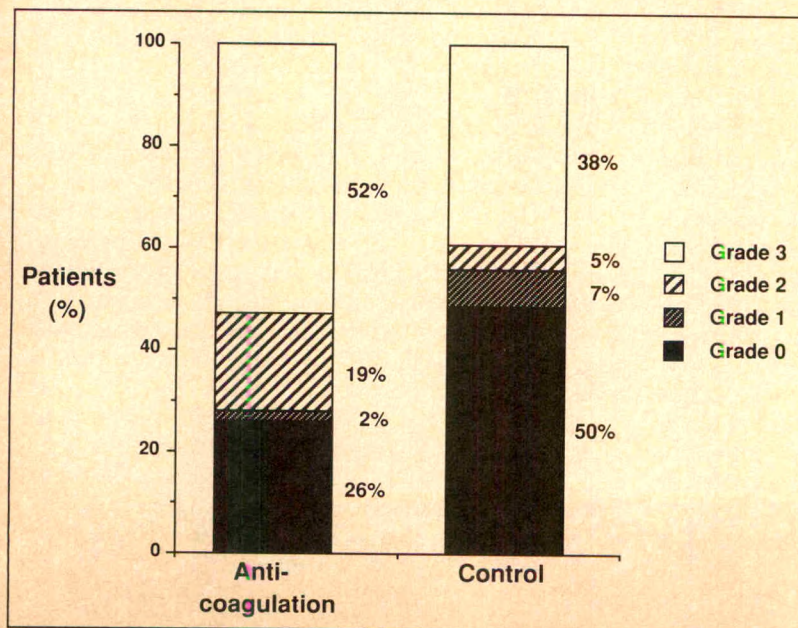


FIGURE 1. Results of angiography. Percentage of patients demonstrating angiographic Thrombolysis in Myocardial Infarction trial flow grades 0 to 3 are shown.

TABLE III Effect of Heparin Therapy on Mortality in ISIS-2 (18)

	Vascular Deaths/Number of Patients (% dead)		
	Streptokinase ± Aspirin	Streptokinase + Aspirin	Streptokinase Only*
Heparin therapy "planned" at entry			
Intravenous heparin	170/2,054 (8.3%)	66/1,024 (6.4%)	104/1,039 (10.2%)
Subcutaneous heparin	325/3,601 (9.0%)	137/1,805 (7.6%)	188/1,796 (10.4%)
No heparin	296/2,937 (10.1%)	140/1,463 (9.6%)	156/1,474 (10.6%)

Note: This was a prespecified subsidiary analysis of the trial.
* Calculated from published data, i.e., first 2 columns of table.

cardial infarction onset.¹⁸⁻²⁰ A corollary conclusion is that preservation of the benefits of early reperfusion depends on prevention of rethrombosis and reocclusion. Symptomatic reocclusion leading to recurrent ischemia and infarction represents the clinically apparent result of failure to maintain arterial patency. However, silent reocclusion has been documented^{7,15} and may result in less readily apparent adverse clinical sequelae, e.g., silent ischemia.

After successful pharmacologic thrombolysis, residual clot and the disrupted endothelium represent potent thrombogenic stimuli that continue to activate the coagulation system.²⁻⁵ The time course of the resolution of this risk is unknown. Empiric pharmacologic approaches to this situation have utilized a low-dose, continuous infusion of a thrombolytic agent, as well as the anticoagulant, heparin, which potentiates the efficiency of antithrombin III, the physiologic inhibitor of thrombin. Results of early trials evaluating the former approach after thrombolysis with rt-PA provided contradictory results: One study indicated that rethrombosis was a significant problem, especially in patients with high-grade residual stenosis, but could be prevented by several hours of a low-dose, continuous, "maintenance" infusion of rt-PA.²¹ In contrast, a randomized study indicated that the rethrombosis rate was low and was similar in patients receiving, compared with those not receiving, a maintenance infusion.²²

Despite these results, the most widely studied and currently recommended rt-PA regimens have included a 2- to 4-hour maintenance infusion aimed at reducing the rethrombosis rate.^{6,7,23,24} In addition, as with other thrombolytic agents, heparin anticoagulation is recommended^{6,12,23,25-29} though the optimal dose, duration and route of administration has not been extensively evaluated. Alternatively, rt-PA has been combined with non-fibrin-selective thrombolytic agents resulting in systemic fibrinogenolysis.^{12,30,31} In these cases, the risk of rethrombosis due to persistent thrombin activity is theoretically reduced by removal of thrombin substrate, i.e., fibrinogen, with generation of fibrinogen degradation products. It has recently been shown that the risk of rethrombosis is inversely correlated with the levels of fibrinogen degradation products which act as potent anticoagulants.³²

Thrombolysis with streptokinase and the role of heparin therapy: Information on the impact of heparin

therapy is available from 6 trials of streptokinase in acute myocardial infarction.^{18,33-37} The major ones include the Subcutaneous Calcium-Heparin in Acute Myocardial Infarction trial, a randomized multicenter study that compared 218 patients receiving streptokinase and intravenous/subcutaneous heparin (2,000 U intravenously at the time of enrollment followed by 12,500 U subcutaneously every 12 hours beginning 9 hours later) with 215 patients treated with streptokinase alone.³³ In-hospital mortality in the group receiving heparin was 4.5% compared with 8.8% in the control group ($p = 0.05$). Recurrent ischemia and reinfarction rates were reduced in the heparin group, but the differences did not reach statistical significance.

In the pilot study for the Second International Studies of Infarct Survival (ISIS-2), 619 patients were randomized in a $2 \times 2 \times 2$ factorial design to streptokinase or placebo, aspirin or placebo and heparin or placebo.³⁴ In this study, heparin was associated with a decrease in reinfarction from 4.9 to 2.2% (difference not significant) but no difference in mortality was observed.

The largest study from which information on heparin therapy is available is ISIS-2.¹⁸ Even though it was designed primarily to evaluate the effects of streptokinase and aspirin on mortality after acute myocardial infarction, the study provides information on the outcome of patients receiving intravenous, subcutaneous or no heparin therapy. In all patients randomized to streptokinase and aspirin, mortality at 5 weeks was highest in patients receiving no heparin (9.6%), lower in those receiving subcutaneous heparin (7.6%) and lowest in those receiving intravenous heparin (6.4%) (Table III). Interestingly, the beneficial effect of heparin was limited to patients receiving aspirin in addition to streptokinase, whereas the beneficial effect of aspirin observed in this study was much greater in patients receiving heparin after streptokinase than in those not receiving heparin (Table III). This suggests an interaction between heparin and aspirin after thrombolysis with streptokinase.

Though not conclusive, these data suggest that anticoagulation with heparin may lead to increased bleeding but also may play an important contributory role in the reduction of mortality seen after streptokinase therapy. It appears that intravenous heparin is more effective than subcutaneous heparin, but that subcutaneous heparin may also exert a positive effect after streptokinase therapy. In light of the evidence supporting the impor-

tance of a patent infarct artery during recovery from acute myocardial infarction, it is probable that heparin exerts this effect through reduction in the incidence of rethrombosis and reocclusion, whether silent or clinically apparent, or through acceleration of the spontaneous thrombolysis that occurs after acute myocardial infarction.^{38,39} If aspirin exerts beneficial effects through longer term prevention of reocclusion, more pronounced effects would be expected in patients with infarct artery patency initially maintained by heparin.

Thrombolysis with recombinant tissue-type plasminogen activator and heparin therapy: Sufficient data to evaluate fully the role of heparin (or aspirin) on the outcome of patients with acute myocardial infarction after treatment with rt-PA are not available. In the current study, although aspirin therapy was precluded after patient enrollment, a limitation of the protocol was that aspirin use before enrollment was not controlled. The potential impact of prior aspirin use on the observed results is unknown.

A recent study in Australia treated patients with acute myocardial infarction with 100 mg of rt-PA over 3 hours and intravenous heparin for 24 hours and then they were randomized to either continuation of intravenous heparin in 99 patients or conversion to aspirin and dipyridamole in 103 patients until coronary angiography was performed at 1 week.⁴⁰ The investigators concluded that anticoagulant therapy with intravenous heparin could be effectively and safely replaced with antiplatelet therapy as early as 24 hours after rt-PA. A small, randomized study also suggested that in many patients, after 24 hours, heparin does not protect against rethrombosis and does contribute to bleeding.⁴¹

Another study, the Heparin-Aspirin Reperfusion Trial (HART) was recently completed in over 200 patients comparing rt-PA plus heparin with rt-PA plus aspirin.⁴² Utilizing angiography performed early (7 to 24 hours) and late (7 to 10 days), their preliminary data support an important early role for heparin anticoagulation in preserving infarct coronary patency after rt-PA therapy of acute myocardial infarction. In addition, this study confirms the relative effectiveness of aspirin in maintaining coronary patency during the period beginning 24 hours after thrombolysis and ending at 1 week.

Although not conclusive, the data on anticoagulation after thrombolysis with rt-PA and streptokinase suggest that the role of antithrombin therapy with heparin may be even more necessary to a favorable clinical outcome with rt-PA than with streptokinase because of 2 important pharmacologic factors: half-life and fibrin-selectivity. The elimination half-life of rt-PA is on the order of 5 minutes, while that of streptokinase is about 25 minutes. After the termination of the infusion, rt-PA is cleared from the blood within 30 minutes, while streptokinase circulates for several hours. If the importance of anticoagulation after rt-PA therapy is confirmed, the half-life of rt-PA may dictate the optimal time for initiation of such therapy. Fibrinogen degradation products are potent anticoagulants that are produced by the action of plasmin on fibrinogen.³² The concentration of degradation products produced after therapy with the non-fibrin-selective agent streptokinase is over 2.5 times

higher than that after the relatively fibrin-selective agent rt-PA, leading to a more pronounced and a more extended anticoagulant effect.⁴³

Implications of current study: The current study suggests that heparin anticoagulation preserves coronary arterial patency after successful thrombolysis with rt-PA while modestly increasing the risk of minor bleeding complications after acute myocardial infarction. The magnitude of the difference observed in arterial patency rates (71 and 44%) was not reflected by a comparable difference in the incidence of clinical reocclusion (7.1 and 11.9%). This may have been due to the fact that this pilot study lacked the statistical power to detect this difference.

Alternatively, these results may reflect the physiologic implications of a patent infarct artery during the acute compared to the recovery phase of acute myocardial infarction. During the initial phase of acute myocardial infarction, symptomatic ischemia and necrosis occur because of the imbalance between increased myocardial oxygen demand and decreased coronary blood flow. Successful thrombolysis acutely restores blood flow to a level sufficient to interrupt the ischemic process. Hours or days later, with myocardial oxygen demand returned to baseline levels because of normalization of heart rate and blood pressure, a reduction in coronary blood flow due to rethrombosis may not reproduce an oxygen supply-demand imbalance sufficient to cause recurrent symptoms in all cases. Recruitment of collateral circulation to the jeopardized zone may also play a protective role.¹⁹

The findings of the TAMI heparin trial combined with the results of this study and the preliminary report of the HART study imply that subacutely (i.e., up to 24 hours), after thrombolytic therapy with rt-PA, in the absence of adequate heparin anticoagulation, silent reocclusion may occur in a significant number of patients. The National Heart Foundation and HART studies further suggest that after 24 hours the need for aggressive anticoagulation diminishes. Since the large majority of infarct arteries are patent 10 to 14 days after myocardial infarction whether or not thrombolytic therapy has been administered, the so-called "catch-up" phenomenon,^{17,39} such reocclusion may be transient and may be associated with initially subclinical sequelae, e.g., silent ischemia. Other studies are required to confirm the findings of this pilot study, to evaluate more fully the prognostic significance of silent reocclusion and to determine the adequate dose, timing and method of anticoagulation after thrombolysis with rt-PA.

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Usefulness of a Pericardial Friction Rub After Thrombolytic Therapy During Acute Myocardial Infarction in Predicting Amount of Myocardial Damage

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To evaluate the clinical incidence and outcomes of patients with pericarditis after thrombolytic therapy, 810 patients were prospectively studied during acute myocardial infarction (AMI). Pericarditis was defined as the presence of a pericardial friction rub during the hospital course. Only 5% of patients developed a rub during AMI, a low percent compared with that in the prethrombolytic era. A pericardial friction rub more often occurred in the setting of an anterior wall AMI. Patients with, compared to those without, a pericardial friction rub had lower ejection fractions (45 vs 51%, $p = 0.002$); worse regional left ventricular function (-3.2 vs 2.7 , standard deviation per chord); higher in-hospital mortality (15 vs 6%, $p = 0.056$); a higher frequency of power failure (83 vs 57%); a higher frequency of anterior wall location of the AMI (53% of cases, $p = 0.002$); and a higher frequency of 3-vessel disease. Therefore, although the frequency of a pericardial friction rub was low (5%) compared with that in the prethrombolytic era, its occurrence denotes more extensive myocardial damage with a worse clinical outcome. Perhaps with successful reperfusion of the infarct-related vessel, transmural myocardial necrosis is prevented and with it the development of pericarditis. Cardiac tamponade did not occur clinically in any patient who developed a pericardial friction rub.

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Before the era of thrombolytic therapy, pericarditis in acute myocardial infarction (AMI) was reported to occur in approximately 7 to 20% of patients.¹⁻⁶ Based on clinical and pathologic studies, the presence of extensive transmural necrosis was believed to be a prerequisite for the development of pericardial inflammation.⁷ Hospital and long-term mortality has been reported to be higher in conservatively treated patients with evidence of pericarditis after AMI.³⁻⁵ By achieving early reperfusion, the use of thrombolytic therapy may prevent progression to transmural necrosis, thereby reducing the risk of developing pericarditis.⁸ Once an inflammatory reaction has developed, the risk of the development of hemorrhagic pericardial tamponade may be increased.⁹ Although pericarditis has been previously reported to occur less frequently in patients given thrombolytic therapy in the setting of AMI,¹⁰⁻¹² the frequency and clinical outcomes of pericarditis after this treatment has not been systematically studied. This study reports the cumulative Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study's experience with pericarditis in the setting of thrombolytic intervention.

METHODS

Patients: Patients with AMI complicated by pericarditis were identified in the TAMI trials 1 through 3 and in the Urokinase Pilot Study at Duke University Medical Center. Pericarditis was strictly defined as the presence of a pericardial friction rub on auscultation on physical examination at any time during the patient's hospitalization. The patients were examined at least daily by the attending physician and study nurses.

As previously described, patients with AMI were prospectively enrolled in trials of intravenous thrombolytic therapy if they met the standard treatment criteria.¹³⁻¹⁶ Briefly, inclusion criteria included: (1) symptoms consistent with an AMI for 30 minutes' duration without response to sublingual nitroglycerin, (2) ST-segment elevation of >1 mm in ≥ 2 contiguous electrocardiographic leads, (3) onset of chest discomfort within 6 hours of the time of thrombolytic therapy administration, and (4) age <76 years. Usual exclusion criteria included: (1) no bleeding diathesis, (2) absence of cardiogenic shock, and (3) no prior coronary artery bypass surgery.

From the Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina; The University of Michigan Medical Center, Ann Arbor, Michigan; Riverside Methodist Hospital, Columbus, Ohio; and Christ Hospital, Cincinnati, Ohio. This study was supported in part by Research Grant HS05635 from the Agency for Health Care Policy and Research, Rockville, Maryland, and Research Grant HL36587 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received May 10, 1990; revised manuscript received and accepted August 1, 1990.

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TABLE I Thrombolytic Regimens

Study	Pharmacologic Regimen	Patients
TAMI 1	rt-PA (150 mg) \pm PTCA	386
TAMI 2	rt-PA + urokinase (variable doses)	147
TAMI 3	rt-PA (135–150 mg) \pm heparin	175
Urokinase	Urokinase (3 million units)	102
Total		810

PTCA = percutaneous transluminal coronary angioplasty; rt-PA = recombinant tissue-type plasminogen activator; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction trial.

TABLE II Pericardial Rub and Thrombolytic Therapy Incidence

Study	No. of Patients	Patients Developing Pericardial Rub
TAMI 1	386	21 (5%)
TAMI 2	147	1 (1%)
TAMI 3	175	16 (9%)
Urokinase	102	2 (2%)
Total	810	40 (5%)

TAMI = Thrombolysis and Angioplasty in Myocardial Infarction trial.

Therapeutic regimens: The 4 thrombolytic therapy trials with their respective pharmacologic interventions are displayed in Table I.^{13–16} As previously reported, after immediate catheterization, all patients were treated with standard therapy including lidocaine, oxygen, morphine as needed for pain and nitrates either topically or intravenously. Aspirin, 325 mg/day, was also administered along with a continuous infusion of intravenous heparin to maintain the partial thromboplastin time at 2 times the control value. This infusion was continued until repeat catheterization at 7 to 10 days. Beta blockers were not added to the medical regimen unless clinically indicated for systemic hypertension, supraventricular tachyarrhythmias or noncardiac disorders (e.g., migraine headaches). Patients were also treated with calcium antagonists 3 times a day. Other medications, including antiarrhythmic agents, were used at the discretion of the clinician. No other antiplatelet agents such as dipyridamole were used routinely.

Data analysis: Case report forms were completed by the clinical research nurse coordinators and reviewed by the principal investigator at each site before submission to the Duke Data Coordinating Center. The data were verified independently by study monitors from review of the clinical records.

Throughout the clinical trials reviewed in this report, a consistent database was maintained to allow for assurance about variable definition and recording of events. Values for continuous variables are presented as mean \pm 1 standard deviation (SD) and for discrete variables values are presented as percentages. For discrete variables, comparisons were made by the chi-square test or the Fisher's exact test and by *t* tests for continuous variables. All *p* values presented are 2-sided.

RESULTS

The frequencies of pericardial friction rub for the different studies are listed in Table II. Of 810 patients

TABLE III Baseline Clinical Characteristics

	Pericardial Rub (n = 40)	No Pericardial Rub (n = 770)
Age (years)*	56 (46–65)	57 (49–65)
Men/women	36/4	614/156
Weight (kg)*	84 (72–93)	82 (73–91)
Coronary risk factors + (%)		
Systemic hypertension	43	42
Diabetes mellitus	8	16
Hypercholesterolemia	5	13
Cerebrovascular disease	3	2
Peripheral vascular disease	5	5
Family history of premature coronary artery disease	43	46
Cigarette smoking	60	64

* Figures shown are median (25th to 75th percentiles).

+ = risk factors obtained from admission history. Definitions have been previously published.²⁰

TABLE IV Baseline Angiographic Data

	Pericardial Rub (n = 40)	No Pericardial Rub (n = 770)
AMI location (%)		
Anterior	23 (57)	308 (40)
Inferior	17 (43)	462 (60)
Infarct-related artery (%)		
Left main	1 (2)	1 (0.5)
Left anterior descending	20 (50)	288 (37)
Left circumflex	3 (8)	101 (13)
Right	14 (35)	358 (47)
Graft	1 (2)	4 (0.5)
Undetermined	1 (2)	18 (2)
No. of coronary arteries narrowed 50% in diameter (%)		
0	4 (10)	59 (8)
1	16 (40)	362 (47)
2	7 (17)	217 (28)
3	12 (30)	126 (16)
Left main	1 (3)	6 (1)
TIMI grade 90 minutes consensus (%)		
Patent	28 (72)	539 (72)
Occluded	11 (28)	208 (28)
0	7 (18)	158 (21)
1	4 (10)	50 (7)
2	5 (13)	156 (21)
3	23 (59)	383 (51)

AMI = acute myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction trial.

examined, 40 (4.9%) had evidence of clinical pericarditis during the hospitalization. The variability among the different phases of the thrombolytic studies was not substantial.

Baseline characteristics for patients with or without a pericardial rub did not differ with regard to gender, demographics and standard cardiac risk factors (Table III). Of the 40 cases, 23 (58%) had a rub detected within 48 hours of initial presentation.

Patients with anterior wall AMI had a higher incidence of a pericardial friction rub than those with inferior AMI (Table IV). Similarly, the left anterior descending coronary artery was more often the infarct-related artery in the pericarditis group. Patients who developed a friction rub had more severe coronary dis-

ease than those who did not (33% with 3-vessel or left main disease versus 17%). No difference was apparent in acute catheterization Thrombolysis in Myocardial Infarction study flow grades between those with or without clinical pericarditis.

Patients with clinical pericarditis had a significantly lower global ejection fraction at the time of acute ventriculography (Figure 1): Median global ejection fraction was 45% for those with and 51% for those without ($p = 0.002$). Infarct zone function measured in SDs per chord was significantly worse at the time of catheterization in patients who developed clinical pericarditis (Figure 2). Median infarct zone function (SD per chord) was -3.2 in patients with a pericardial rub compared with -2.7 SD per chord in patients without a pericardial rub ($p = 0.024$). Of these 2 measurements, global left ventricular ejection fraction at baseline catheterization was the most important parameter for predicting the presence or absence of a pericardial friction rub ($p = 0.01$). This finding was independent of infarction location.

When clinical outcomes were examined, patients who developed a friction rub tended to do worse than those who did not (Table V). Hospital mortality was

higher in patients with (15%) compared with those without clinical pericarditis (6%) ($p = 0.056$). In patients with a rub who died, power failure tended to be the predominant mechanism (83%), whereas in patients without a rub, the cause of death was more evenly distributed between power failure (57%) and other factors, mostly arrhythmia. No patient in either group developed a hemodynamically significant pericardial effusion or cardiac tamponade by bedside clinical evaluation. This negative finding has an upper 95% confidence limit of approximately 0.4%.

DISCUSSION

The principal finding of this study is that the incidence of a pericardial friction rub in the setting of thrombolytic therapy for AMI is especially low compared with older studies describing conservatively treated patients.⁵ A pericardial friction rub was only found in 5% of all patients. In contrast, the incidence of pericarditis before the thrombolytic era has been reported to be between 7 and 20%. In the recently reported Multicenter Investigation of the Limitation of Infarct Size study, in which patients did not receive thrombolytic therapy, pericarditis occurred in 20% of those enrolled.⁵

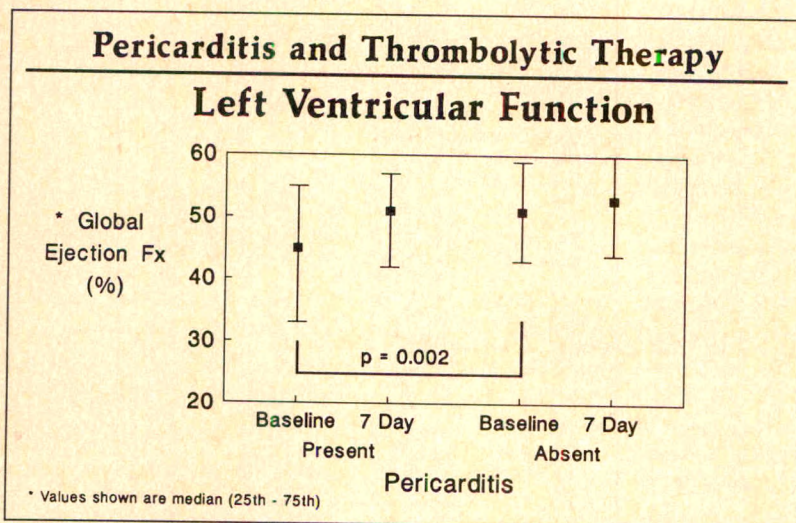


FIGURE 1. Median (25–75th percentile) values for global left ventricular function (%) at baseline and at 7-day follow-up in patients with and without clinical pericarditis. Fx = fraction.

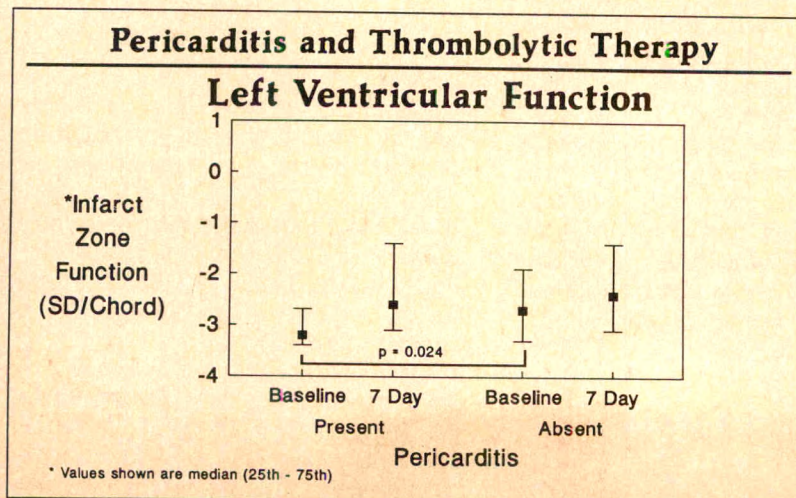


FIGURE 2. Median (25–75th percentile) infarct zone function (standard deviation [SD] per chord) at baseline and at 7-day follow-up in patients with and without clinical pericarditis.

TABLE V Major Clinical Outcomes

	Pericardial Rub (n = 40)	No Pericardial Rub (n = 770)
Mortality (%)	6 (15)	49 (6)
Power failure	5 (83)	25 (51)
Arrhythmia	1 (17)	11 (22)
Sudden death	0	5 (10)
Other	0	8 (16)
Congestive heart failure Killip class (%)		
2	7 (18)	96 (12)
3	4 (10)	32 (4)
4	1 (3)	11 (1)
Reocclusion	6 (15)	92 (12)
Coronary artery bypass grafting		
None	24 (60)	608 (79)
Emergency	5 (13)	38 (5)
Urgent	7 (18)	42 (5)
Elective	4 (10)	81 (11)
Late CABG	0	1 (0.1)
Cardiac tamponade	0	0

CABG = coronary artery bypass graft surgery.

The patients in this study who developed clinical pericarditis had more extensive myocardial damage, as documented by significantly worse baseline global and segmental left ventricular function, more frequent occurrence of anterior wall AMI, and a higher in-hospital mortality as opposed to those without pericarditis. In fact, the degree of left ventricular damage as measured by global ejection fraction predicted the presence of a friction rub independently on infarct location. These findings are consistent with those reported before the thrombolytic era and with the pathologic findings suggesting that transmural extension of myocardial necrosis is a prerequisite for the development of a pericardial friction rub. As recently reported by Sugiura et al¹⁷ patients who develop pericarditis during AMI have a higher pulmonary artery wedge pressure, more advanced degrees of ventricular segmental asynergy and more often have a ventricular aneurysm. Perhaps with successful reperfusion, transmural myocardial necrosis is prevented and with it development of clinical pericarditis. This observation concurs with early canine pathologic studies by Reimer et al¹⁸ describing the wave front model of myocardial necrosis.

The low incidence of a pericardial friction rub in our study concurs with the previous thrombolytic trials for AMI. In the European Cooperative Study, pericarditis occurred in 6.3% of patients treated with recombinant tissue-type plasminogen activator as opposed to 11% of patients treated with placebo. In the Netherlands and the Italian Group for the Study of Streptokinase in Myocardial Infarction studies evaluating intravenous streptokinase versus placebo, clinical pericarditis occurred twice as frequently in patients not treated with thrombolytic therapy for AMI.¹⁰⁻¹² These findings further support the concept that reperfusion of the infarct-related vessel decreases the likelihood of transmural extension of the infarct and hence the occurrence of a pericardial rub.

The fact that no patient with clinical pericarditis in this study developed clinical evidence of cardiac tam-

ponade is of particular importance. This finding is even more remarkable when one considers the fact that these patients were aggressively treated with concomitant anticoagulant and antiplatelet therapy. It is certainly reassuring to know that hemopericardium with tamponade is extremely unusual in this setting despite case reports to the contrary with only heparin.^{4,8,9,19} We do not believe that the development of a pericardial friction rub in this setting is a contraindication for continuation of intravenous heparin.

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Determinants and Significance of Diltiazem Plasma Concentrations After Acute Myocardial Infarction

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A total of 1,975 plasma diltiazem concentrations were obtained from 1,067 patients enrolled in a multicenter secondary intervention study of diltiazem after acute myocardial infarction. To evaluate the determinants and significance of diltiazem concentrations in this patient population, we related drug concentrations to a variety of clinical variables recorded on the case history forms. Multiple linear regression analysis showed that (1) time from the last drug dose, (2) drug dose taken, (3) patient height (an index of lean body weight), and (4) patient age were important determinants of plasma diltiazem concentrations. For an equivalent dose, plasma diltiazem concentrations in a 75-year-old patient were about double those of a 25-year-old patient. Total weight and drug dose prescribed did not significantly affect plasma concentrations. Whereas drug concentrations were higher ($p = 0.01$) among patients with left-sided heart failure, they were not altered by renal dysfunction, hepatic disease or β blockers. Diltiazem concentrations were a significant determinant of diastolic arterial pressure ($p < 10^{-9}$), but neither systolic pressure nor heart rate were significantly related to diltiazem concentration. The overall incidence of adverse experiences was not related to drug concentrations, but the occurrence of second- and third-degree atrioventricular block in the coronary care unit and the need for a temporary pacemaker were substantially higher among patients with a drug concentration > 150

ng/ml (7.4 and 1.9%, respectively) than among patients with lower concentrations (2.6% for atrioventricular block, 0.3% for pacemaker; $p = 0.02$ for each). The risk of atrioventricular block was particularly increased by high diltiazem concentrations in the face of acute inferior infarction. These results suggest that diltiazem's pharmacologic and clinical effects in a large population are concentration-related, and that the consideration of patient size, age, and left ventricular function in selecting a diltiazem dose may allow for effective drug therapy with a reduced likelihood of adverse effects.

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Optimal dose selection for a drug should maximize the chances of benefit while minimizing the risk of adverse drug effects. The relation between plasma drug concentration and drug actions is usually more consistent than the relation between drug dose and concentration. Much of the variability in response to a drug is due to factors that alter the plasma concentration for a given dose. Pharmacokinetic studies attempt to identify and quantify such factors.

Dose recommendations for diltiazem therapy are generally presented in terms of a range of daily doses, without specific suggestions for dose modification according to patient characteristics.^{1,2} Diltiazem is eliminated by hepatic biotransformation³ with a large first-pass effect,⁴⁻⁶ and renal failure has little effect on its disposition.^{7,8} Diltiazem is substantially bound to plasma proteins,^{9,10} and there is evidence that diltiazem metabolism is altered in the elderly.^{11,12}

There is a need for an evaluation of the factors governing the relation between drug dose and concentration within specific patient populations receiving drug therapy. In a recent randomized study,¹³ 1,234 patients were allocated to active treatment with diltiazem. As part of the study protocol, blood samples were obtained for subsequent plasma diltiazem concentration measurement. Extensive clinical information was recorded during follow-up. If clinical factors that control diltiazem concentrations can be identified from information in this data base, and concentrations are found to determine beneficial, or adverse drug responses, or both, then consideration of such factors in deciding on an initial drug dose

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would be rational. The purpose of the present study was to evaluate the determinants and potential importance of plasma diltiazem concentrations among patients enrolled in the Multicenter Diltiazem Postinfarction Trial.

METHODS

Overall trial design: The design and primary end point analysis of the Multicenter Diltiazem Postinfarction Trial have been described in detail elsewhere.¹³ In brief, 2,466 patients were randomly allocated to receive either diltiazem or identical placebo tablets in a double-blind fashion. Entry criteria included age between 25 and 75 and documented acute myocardial infarction.¹³ Exclusion criteria were: ongoing cardiogenic shock or hypotension; pulmonary hypertension; second- or third-degree atrioventricular block; a resting heart rate <50 beats/min; childbearing potential without contraceptive therapy; Wolff-Parkinson-White syndrome; calcium antagonist therapy; a potentially lethal noncardiac disease; nonatherosclerotic myocardial infarction; cardiac surgery; and residence outside the study area. Informed consent was obtained from all enrolled patients. Randomization was stratified to balance groups with respect to time after myocardial infarction, use of β blockers, and New York Heart Association classification.

Clinical variables, including vital signs, a medical history and a physical examination, were recorded at entry into the trial and at each clinic visit. Chest x-rays in the coronary care unit were interpreted by the radiology department of each center. For each patient, study coordinators identified the x-ray report of the greatest severity of pulmonary congestion and graded the congestion on a 4-level scale of severity (no, mild, moderate, or severe congestion).¹³

Drug therapy and plasma concentration measurements: Therapy was initiated with diltiazem (60 mg) or identical-looking placebo tablets 4 times/day. Dose adjustments and trial drug discontinuation were at the discretion of the treating physician. Blood samples for drug assay were to be obtained whenever possible, within a month of entry into the trial, within 6 months of entry and at the conclusion of the study. Because of a variety of technical factors (patient refusal, samples broken in transit, and so forth), blood levels were not available for all patients at each time point. The interval from last dose to sampling time varied widely (Figure 1), although trough samples were to be obtained whenever possible. Plasma was removed from each sample within 30 minutes, frozen at -4°C , and shipped frozen to Marion Laboratories, Kansas City, Missouri, for diltiazem assay using high-performance liquid chromatography techniques.

Statistical analysis: Correlations were analyzed by simple or multiple linear regression, with statistical significance determined by analysis of variance or covariance.¹⁴ Comparisons between group means were performed by *t* tests when each of the 2 groups had ≥ 30 members.¹⁴ Otherwise, a nonparametric test (Wilcoxon) was used.¹⁴ Contingency data were analyzed by chi-square or by Fisher's exact test.¹⁴ Group data are

presented as mean \pm standard error, and a statistically significant difference was defined as $p < 0.05$.

For the analysis of the relation between drug concentration and physiologic variables (e.g., heart rate, blood pressure), plasma concentrations for each patient were matched to measurements obtained at the same clinic visit. Because the temporal relation between adverse experiences and blood sampling was complex and variable, we restricted the analysis of the relation between adverse experiences and plasma concentrations to the initial hospitalization. Other analyses were based on samples obtained at a specific month after trial entry, or on the first plasma concentration in each patient when only 1 representative sample per patient was to be analyzed.

RESULTS

Diltiazem concentrations were measurable in 1,975 samples from 1,067 patients. Nine hundred forty-nine patients with measurable concentrations had been randomized to diltiazem; 118 patients with detectable concentrations were receiving open-label diltiazem.

Determinants of diltiazem concentrations: Diltiazem concentrations ranged from 7 to 691 ng/ml (mean 133). Time from the last dose of diltiazem was an important determinant of plasma drug concentration, as shown in Figure 2. Plasma concentrations rose over the first 2 hours after a dose, remained stable for about 4 hours, and then declined in a log-linear fashion with a half-life of 5.89 hours.

The factors determining plasma diltiazem concentration were evaluated by multiple linear regression analysis. Data from the 1-month, 6-month and trial close-out clinic visits were examined to determine the relation between drug concentration (as a dependent variable) and drug dose (both prescribed and actual dose taken), the interval from the last dose, and patient height, weight and age (potential independent variables). As summarized in Table I, the significant determinants of diltiazem concentration included the dose taken, the interval from the last dose, patient height and patient age. Patient weight and the dose prescribed were

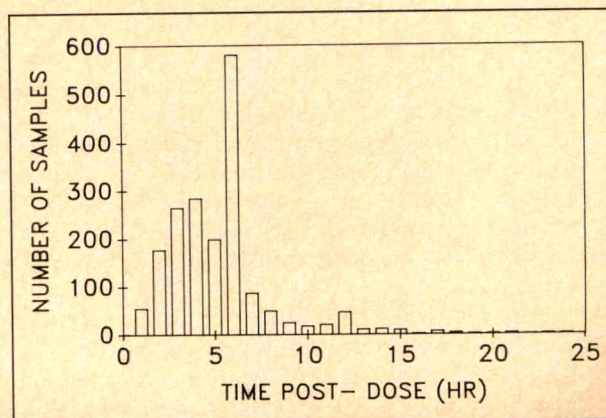


FIGURE 1. Number of plasma samples available at each time interval from the last dose of diltiazem. HR = hours.

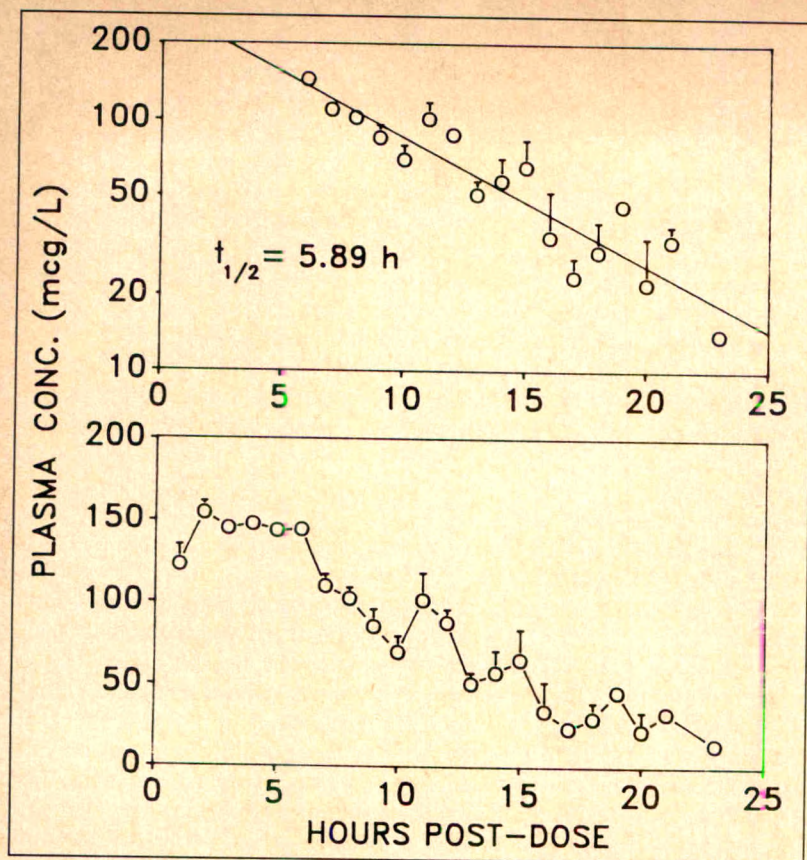


FIGURE 2. Mean \pm standard error of plasma diltiazem concentration (PLASMA CONC.) as a function of time interval from last drug dose. Direct plot is shown on bottom, and a log-linear plot of the same data on top. Least-squares regression line to log-linear plot indicates a plasma half-life of 5.89 hrs (h).

TABLE I Multiple Linear Regression Analysis for Factors Determining Plasma Diltiazem Concentration

Variables	Six-Month Samples (n = 372)			One-, Six-Month and Closeout Analysis (n = 1,220)		
	Coefficient	t	p Value	Coefficient	t	p Value
Intercept	209	2.3	0.02	155	3.2	0.001
Interval (hour)	-6.0	-5.0	<0.0001	-6.9	-10.2	<0.0001
Dose prescribed (tablets/day)	-2.3	-0.2	0.82	10.9	2.1	0.03
Dose taken (tablets/day)	25.3	3.7	0.0002	17.2	4.9	<0.0001
Weight (lb)	0.2	1.5	0.13	0.05	0.7	0.51
Height (in)	-3.5	-2.8	0.005	-2.4	-3.6	0.0004
Age (yr)	1.2	3.0	0.003	1.1	5.1	<0.0001

For the 6-month analysis, $r = 0.41$, $F_{6,354} = 12$, $p = 3 \times 10^{-12}$.

For the 1-, 6-month and closeout analysis, $r = 0.39$, $F_{6,1213} = 37$, $p < 10^{-30}$.

All values used for regression analysis were recorded for the clinic visit at which plasma was obtained for subsequent drug assay. Height was used as an index of ideal body weight. Results are shown for the midtrial data only (6 months, left), and for samples obtained at 1-, 6-month and closeout analysis (right).

not important contributors to the regression. The regression of plasma diltiazem concentration on the 4 aforementioned significant variables accounted for about 16% of the overall variance in plasma concentrations ($r = 0.4$), as shown in Figure 3. Patient height was used as an index of lean body mass—the substitution of body surface area,¹⁵ body mass index ($\text{weight}/\text{height}^2$) and ponderosity index ($\text{weight}/\text{height}^3$) weakened the multilinear regression.

Patients with pulmonary congestion in the coronary care unit had a mean diltiazem concentration of $188 \pm 10 \text{ ng/ml}$, which is higher than the mean concentration of $160 \pm 6 \text{ ng/ml}$ ($p = 0.01$) measured in patients without pulmonary congestion. There was a graded relation between the severity of pulmonary congestion and diltiazem

plasma concentration (Figure 4). On the other hand, current β blocker therapy, and renal or hepatic disease did not alter diltiazem concentration. Pulmonary congestion in the coronary care unit was not a predictor of subsequent outpatient diltiazem concentrations.

Relation between plasma concentrations and diltiazem actions: PHARMACOLOGIC AND THERAPEUTIC ACTIONS: Heart rate and systolic pressure at each clinic visit were not correlated with drug concentrations. However, there was a highly significant negative correlation between diastolic pressure and diltiazem plasma concentration ($F = 17.4$, $DF = 1/1,817$, $p < 10^{-9}$). There was no apparent relation between drug concentrations and the occurrence of angina, nitroglycerin consumption, the in-

cidence of coronary bypass surgery, or the prevalence of congestive heart failure.

ADVERSE EXPERIENCES: Adverse experiences were reported as a part of routine monitoring. Diltiazem plasma concentrations during the initial hospitalization were compared between patients with and without adverse experiences during the hospitalization. The total number of adverse experiences was not related to drug concentrations. Second- or third-degree atrioventricular block was reported as an adverse experience in 8 patients, whose diltiazem concentrations (220 ± 28 ng/ml) were higher than those of patients without atrioventricular block (162 ± 7 ng/ml, $p < 0.05$). Among the 7 patients in whom the adverse experience of atrioventricular block was felt to be probably or definitely drug-related (excluding 1 patient in whom it was reported as probably not drug-related), the mean diltiazem plasma concentration was 263 ± 26 ng/ml. The case report forms also included the routine reporting of second- or

third-degree atrioventricular block in the coronary care unit irrespective of any suspected relation to trial medication. The median drug concentration for all patients was approximately 150 ng/ml. The likelihood of having second- or third-degree atrioventricular block was significantly greater among patients with a plasma concentration >150 ng/ml, compared to the corresponding risk among patients with a plasma concentration <150 ng/ml (Figure 5). Similarly, the need for a temporary transvenous pacemaker was more frequent among patients with a blood level >150 ng/ml (1.9%), compared with those with a plasma concentration <150 ng/ml (0.3%, $p = 0.02$).

Multivariate analysis was used to explore further the influence of high diltiazem concentrations on the occurrence of atrioventricular block in the coronary care unit. Atrioventricular block was more frequent among patients with inferior myocardial infarctions ($p = 0.002$) and among patients older than the median age of 59 ($p = 0.03$). There was an important interaction between these factors and diltiazem concentration, with atrioventricular block being more common among patients with inferior myocardial infarctions and high plasma drug

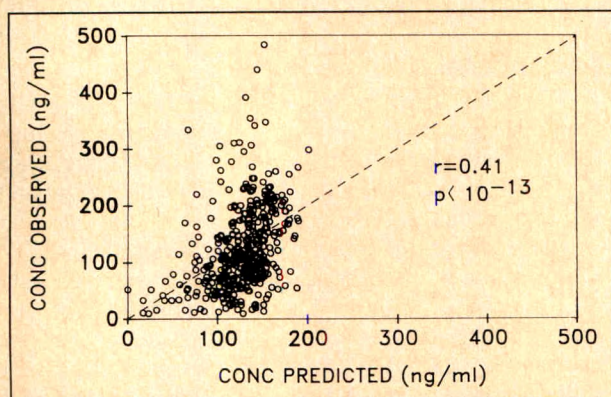


FIGURE 3. Relation between observed plasma diltiazem concentrations (CONC.) after 6 months of therapy and the values predicted by multiple linear regression analysis incorporating the 4 significant determining variables. Regression line had a slope of 0.997, an intercept of 0.4 ng/ml, and a correlation coefficient of 0.41 ($F_{4,376} = 18.5$, $p < 10^{-13}$).

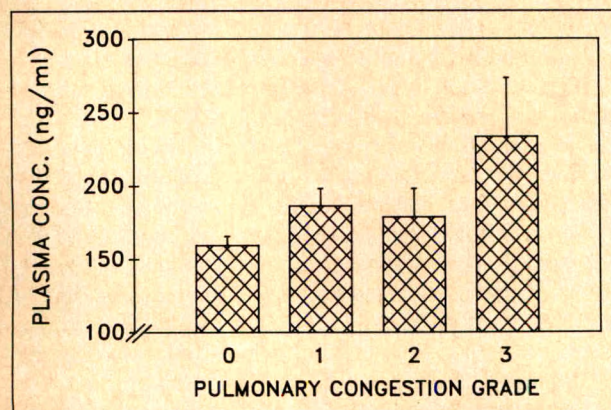


FIGURE 4. Mean \pm standard error of diltiazem plasma concentration (CONC.), as a function of severity of pulmonary congestion on coronary care unit chest x-rays. Severity of congestion was graded from 0 (no pulmonary congestion) to 3 (severe congestion). Pulmonary congestion grade was a significant determinant of diltiazem concentration ($p = 0.05$ by analysis of variance).

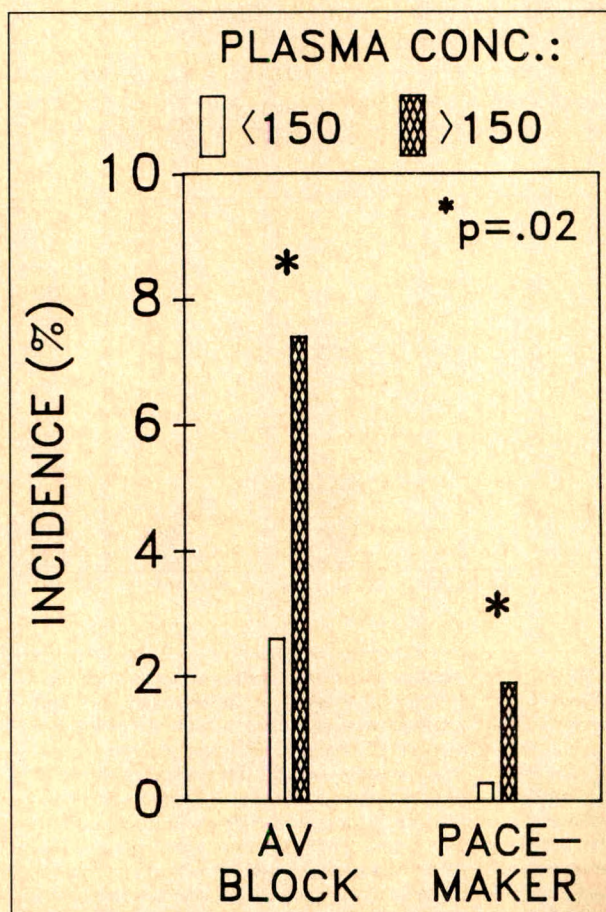


FIGURE 5. Incidence (%) of second- or third-degree atrioventricular (AV) block and requirement for a temporary pacemaker in relation to plasma diltiazem concentration (CONC.). Patients with concentrations in excess of 150 ng/ml were much more likely to develop significant atrioventricular block.

TABLE II Mortality Among Patient Groups According to Diltiazem Plasma Concentration

Concentration Quartile(s)	Plasma Conc. (ng/ml)	Deaths/Patients (% mortality)	
		No Congestion	Pulmonary Congestion
1*	39 ± 1	11/192 (5.7)	12/41 (29.3)
2-3	100 ± 1	19/389 (4.9)	16/89 (18.0)
4	216 ± 9	11/182 (6.0)	6/41 (14.6)

* Patients were divided into quartiles according to the distribution of plasma drug concentrations at each hour after administration. Patients in the lowest quartile (quartile 1) had the lowest concentrations, whereas those in the highest quartile (4) had the highest concentrations. Quartiles 2 and 3 had intermediate concentrations and similar results; data for them was thus combined. Mortality was not statistically significantly different among groups with different plasma drug concentrations. Conc. = concentration.

concentrations, and particularly common among older patients with inferior myocardial infarctions and high plasma drug concentrations ($p < 0.05$, Figure 6). The presence of anterior myocardial infarction or β blocker therapy did not increase the incidence of atrioventricular block. For a variety of other cardiovascular adverse experiences, including unstable angina, atrial bradycardia, hypotension, pulmonary congestion and congestive heart failure, plasma diltiazem concentrations were not different for patients with an adverse experience compared to those without it.

PRIMARY END POINT ANALYSIS: Primary end point analysis of the trial suggested a bidirectional interaction between the presence of pulmonary congestion and the

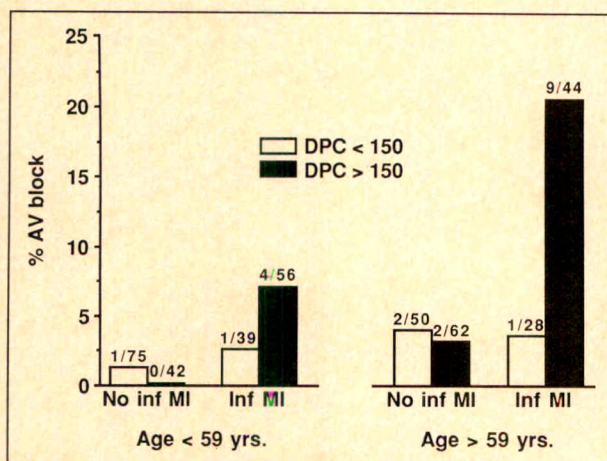


FIGURE 6. Frequency (%) of occurrence of second- or third-degree atrioventricular (AV) block in the coronary care unit, as a function of patient age, presence or absence of inferior myocardial infarction (inf MI), and diltiazem plasma concentration (DPC). Fractions above each bar indicate number of patients developing atrioventricular block (numerator) and total number of patients in the group represented (denominator). While inferior myocardial infarction, older age and higher drug concentration were each associated with an increased likelihood of atrioventricular block, there was a significant interaction among these factors, in that patients with inferior myocardial infarctions and high drug concentrations, particularly the older age group, accounted for most of the increased risk in each category. Patients with only 1 of these risk factors did not have a markedly higher rate of occurrence of atrioventricular block.

effects of diltiazem on mortality.¹³ Patients without pulmonary congestion had a lower mortality rate when treated with diltiazem, whereas patients with pulmonary congestion randomized to diltiazem had a higher mortality rate than those receiving placebo. To determine whether this interaction was related to plasma drug concentration, we divided patients into plasma concentration quartiles. Because time from the last dose of diltiazem was a major determinant of plasma concentration, we determined the concentrations of diltiazem that divided the distribution of concentrations into quartiles at each hourly interval after drug administration. Patients were thus assigned to groups based on whether their plasma drug concentrations fell into the highest quartile, lowest quartile, or middle half of the plasma concentration distribution within the cohort of samples drawn at the same time relative to drug ingestion. As summarized in Table II, the mortality rate was not increased in patients with higher drug concentrations and pulmonary congestion compared to those with lower concentrations.

DISCUSSION

We found that a variety of factors determine diltiazem plasma concentrations in a postinfarction population. Furthermore, plasma concentrations of the drug bear an important relation to a variety of therapeutic and toxic effects.

Determinants of plasma concentration: The major determinants of diltiazem concentration were the interval from the last drug dose, the dose taken, height, age and left ventricular dysfunction as indicated by pulmonary congestion. Diltiazem concentrations decreased with a half-life of 5.9 hours, a value similar to the mean half-life (4.8 hours, range 3.4 to 7.4) previously reported.^{4-8,11,16} A first-order decline in diltiazem concentration was not observed in our patients until 6 hours after an oral dose. A similar phenomenon has been noted in another study,⁴ and is explained by continuing enteric absorption for several hours. Because of continued absorption, plasma concentrations do not decrease by 50% until about 10 hours after an oral dose, explaining the clinical efficacy of diltiazem given at intervals substantially longer than its elimination half-life.

We found it surprising that the diltiazem dose prescribed did not correlate with drug concentration. The reason for this became clearer when we analyzed the dose taken (as estimated by pill counts), and found it to be strongly related to plasma concentrations. Variability in compliance therefore accounted for the poor relation between prescribed dose and blood levels. This emphasizes the importance of pill counts (or plasma concentration measurements, or both) in establishing true dose-related phenomena in a clinical trial.

Patient height was a more important determinant of diltiazem concentration than body weight. This suggests that, although diltiazem is lipid soluble, it is distributed predominantly in lean body mass. Lidocaine, also a very fat-soluble drug, likewise has a volume of distribution that is closely related to lean body weight.¹⁷

Diltiazem concentrations for a given dose increased substantially with age, approximately doubling over the age range from 25 to 75. Previous studies have shown that diltiazem's half-life is longer in elderly volunteers,¹¹ and that diltiazem clearance is reduced in elderly hypertensive patients.¹² The age-dependent disposition of diltiazem resembles that of lidocaine in a similar population.¹⁸ The increase in diltiazem concentrations that we observed in association with evidence of left ventricular dysfunction is also similar to previous observations with lidocaine.¹⁸⁻²⁰ The parallels between the disposition of diltiazem and lidocaine may be due to the high lipid solubility^{4,17} and high-efficiency hepatic metabolism^{3,21} that the compounds share. Heart failure reduces liver blood flow and therefore plasma clearance of such agents,²² resulting in a higher concentration for the same dose.

Significance of diltiazem concentrations: We found that diltiazem concentrations were a significant determinant of diastolic arterial pressure. This is compatible with the concentration-related hypotensive actions of the drug.²³ The lack of concentration-related changes in heart rate and systolic pressure suggests that these are less affected by the compound or are subject to greater variability, which masks diltiazem's contribution. The lack of concentration-related antianginal actions may have been due to a flat dose-response curve,²⁴⁻²⁷ although this has not been a universal finding.^{28,29} Because this study was not designed to detect or to quantify the drug's antianginal properties, no strong conclusions regarding antianginal actions can be drawn.

Diltiazem concentrations were a determinant of the occurrence of atrioventricular block and the need for temporary pacemaker therapy. To our knowledge, this is the first clinical trial to demonstrate that plasma concentration is an important determinant of diltiazem-related atrioventricular block in a postinfarction population. It is in keeping with the previously demonstrated concentration-dependent effects of diltiazem on atrioventricular conduction in experimental animals³⁰ and in man.⁶ Atrioventricular block associated with high diltiazem levels in the coronary care unit was particularly likely among older patients with inferior myocardial infarctions (Figure 6), indicating that such patients are predisposed to this potential complication of diltiazem therapy.

Clinical implications: We found that plasma diltiazem concentrations in a large postinfarction population can be related to important clinical predictors, and that concentrations in turn relate to beneficial and adverse drug actions. These observations support the consideration of factors altering drug concentration in deciding on an initial diltiazem dose, and provide further rationale for clinical practices such as the use of smaller initial doses of diltiazem in the elderly and in patients with left ventricular dysfunction. Our results urge caution in the selection of diltiazem dosages for patients with acute inferior myocardial infarction, particularly for the elderly, because of an increased risk of concentration-related atrioventricular block.

We studied plasma concentrations in order to gain insights into factors that govern the relation between diltiazem dose and clinical actions. Monitoring of plasma concentrations plays at most a small role in guiding diltiazem therapy, and final dose selection in all cases should be based on individual patient responses.

Finally, our results indicate the value of incorporating plasma drug concentration measurements in large clinical drug trials. Along with carefully collected clinical data, the availability of plasma concentrations allows for valuable insights into drug pharmacokinetics and pharmacodynamics in a large patient sample. This information may reflect the patient population treated with the drug in ways that smaller volunteer studies cannot.

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Prehospital Thrombolysis in Acute Myocardial Infarction

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The benefit and risk of prehospital thrombolysis for acute myocardial infarction (AMI) were evaluated in a double-blind randomized trial. Patients presenting <4 hours after symptom onset received 2 million units of urokinase as an intravenous bolus either before (group A, n = 40) or after (group B, n = 38) hospital admission. The mean time interval from onset of symptoms to thrombolytic therapy was 85 ± 51 minutes in group A and 137 ± 50 minutes in group B ($p < 0.0005$). In 91% of the patients, thrombolytic therapy was administered <3 hours after symptom onset. Complication rates during the pre- and in-hospital period were low and did not differ between groups. Three patients died (1 in group A, 2 in group B) from reinfarction 7 to 14 days after admission. Left-sided cardiac catheterization before discharge revealed a patency rate in the infarct-related artery of 61% in group A and 67% in group B (difference not significant). Global left ventricular function and regional wall motion at the infarct site did not differ significantly between group A and B (ejection fraction $51 \pm 10\%$, n = 28 vs $53 \pm 14\%$, n = 28; wall motion -2.3 ± 1.3 vs -2.2 ± 1.1 standard deviation, respectively). Also, peak creatine kinase did not differ significantly (838 ± 634 U/liter in group A vs 924 ± 595 U/liter in group B). Prehospital thrombolysis using a bolus injection of urokinase has a low risk when performed by a trained physician with a mobile care unit. The saving of 45 minutes in the early stage of an acute infarction through prehospital thrombolysis did not appear to be important for salvage of myocardial function.

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It is known from experimental and clinical studies that the time from onset of acute myocardial infarction (AMI) to reperfusion is a major determinant of myocardial salvage and mortality.¹⁻³ Uncontrolled clinical studies have suggested the possible value of prehospital thrombolysis, achieved by starting therapy in a mobile care unit.^{4,5} However, the possible benefit of prehospital thrombolysis may be outweighed by an increased risk. This article presents the data of the first double-blind randomized trial evaluating the risk and benefit of prehospital thrombolysis in AMI.

METHODS

Patients: Seventy-eight patients (66 men, 12 women, mean age \pm standard deviation 55 ± 8 years) who met the following criteria were included in the study: (1) severe chest pain typical for myocardial ischemia lasting >30 minutes, (2) arrival of the ambulance doctor within 4 hours after the onset of symptoms, (3) ≥ 2 mm of ST-elevation in ≥ 2 electrocardiographic leads for inferior AMI and ≥ 3 mm of ST-elevation in ≥ 2 precordial leads for anterior AMI, (4) age ≤ 70 years, (5) no prior AMI, and (6) no contraindications against thrombolysis.

Study protocol: The protocol is shown in Figure 1. The mobile care units used in the study were staffed with a physician and 2 emergency medical technicians. A portable electrocardiograph (Cardioteest, Hellige, Freiburg, Federal Republic of Germany) and resuscitation equipment were available. For randomization and double-blind thrombolytic therapy, Medac (Hamburg, Federal Republic of Germany) prepared numbered pairs of ampules containing either urokinase in ampule A and placebo in ampule B, or vice versa. After informed consent was obtained, a peripheral intravenous line was placed, and the patient was randomly assigned to the next in the series of ampule pairs. The contents of ampule A were dissolved in 20 ml of injectable water as fast as possible. After hospital admission a 12-lead electrocardiogram was recorded and the patient was reevaluated by the hospital doctor. Patients who still met the electrocardiographic inclusion criteria and had no contraindications to thrombolytic therapy received an intravenous injection of ampule B followed by heparin (1,000 U/hour). The patient was then transferred to the intensive care unit. Blood samples were drawn for creatine kinase measurements at routine time intervals (every 4 to 8 hours for the first 24 hours). Coronary and left ventricular angiography were performed before hos-

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TABLE I Comparison of Baseline Characteristics in Patients Randomized to Prehospital Versus In-Hospital Thrombolytic Therapy

	Prehospital	In-Hospital
No. of patients	40	38
Age, years (mean \pm SD)	57 \pm 7	55 \pm 8
Anterior AMI (%)	47	32
Number of narrowed coronary arteries (%) [*]		
1	53 (31) [†]	38 (30)
2	40 (31)	41 (30)
3	7 (31)	21 (30)
Initial clinical status		
Blood pressure (mm Hg)		
Systolic (mean \pm SD)	141 \pm 23 (39)	137 \pm 32
Diastolic (mean \pm SD)	86 \pm 14 (39)	82 \pm 17
Cardiogenic shock (%)	6	6
Pulmonary congestion (%)	17	14
Resuscitation (%)	5	3

^{*} Disease \geq 50% diameter stenosis.
[†] Where data are incomplete, the number of observations is indicated in parentheses.
AMI = acute myocardial infarction; SD = standard deviation.

pital discharge unless clinical instability necessitated earlier catheterization.

Evaluation of clinical status and complications: Clinical status and complications were closely observed during transportation and in the hospital. The electrocardiogram was continuously monitored during transportation. Bleeding complications were recorded by site and need for blood transfusion. Reinfarction was defined as a new onset of symptoms combined with typical electrocardiographic changes or a secondary peak of creatine kinase to more than twice the upper limit of normal, or both.

Analysis of coronary angiograms and left ventricular function: All angiograms were analyzed at the University of Washington. The infarct artery was identified from the location of (1) ST elevation on the electrocardiogram; (2) hypokinetic wall motion in the ventriculo-

TABLE II Acute Myocardial Infarction: Prehospital Versus In-Hospital Thrombolysis

	Time Intervals		p Value
	Prehospital Group (n = 40)	In-Hospital Group (n = 38)	
Onset of symptoms	52 min	63 min	NS
→ call of ambulance	(\pm 47)	(\pm 46)	
Call of ambulance	33 min	31 min	NS
→ first injection	(\pm 15)	(\pm 12)	
First injection	27 min	29 min	NS
→ admission	(\pm 14)	(\pm 13)	
Admission	14 min	14 min	NS
→ second injection	(\pm 13)	(\pm 13)	

NS = not significant.

gram; and (3) residual stenosis or thrombotic material, or both, in the coronary artery.

Coronary artery patency was defined as complete filling of the suspected infarct artery with a delayed or normal runoff of the contrast medium. (Thrombolysis in Myocardial Infarction Trial perfusion grade 2 or 3). Coronary angiograms were assessed by 2 independent observers. Left ventricular function was measured from tracings of the end-diastolic and end-systolic endocardial contours by the area-length and centerline methods, respectively.^{6,12}

Statistics: For calculation of differences between the groups, the Mann-Whitney test was used.

RESULTS

Accuracy of the diagnosis: In 1 patient the diagnosis of an AMI could not be confirmed at hospital admission. He had a pulmonary embolism, and his data were not included in the present analysis.

Comparison between the groups: Of the 78 patients, 40 were randomized to receive the 2 million units of urokinase at home before hospital admission (group

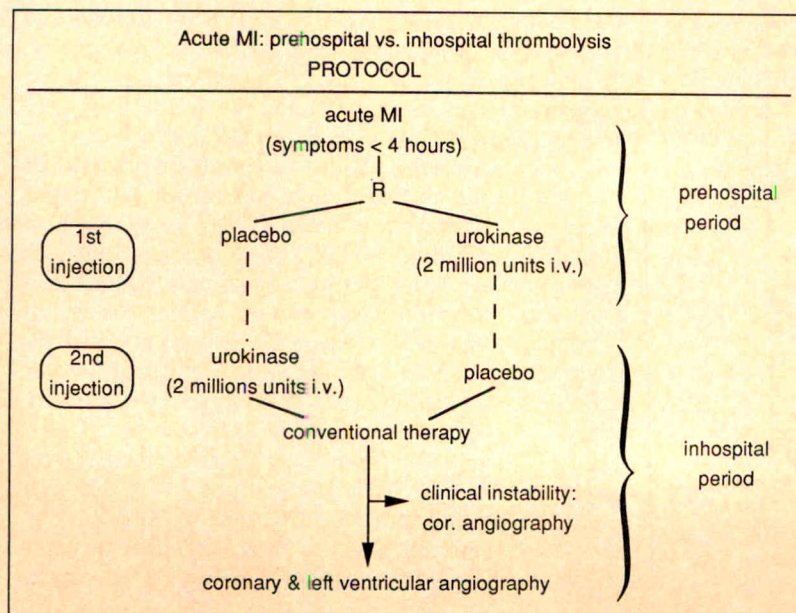


FIGURE 1. Study protocol. cor. = coronary; MI = myocardial infarction; i.v. = intravenous.

A) and 38 patients were treated in the hospital (group B). Both patient groups were comparable at baseline (Table I). In particular, the incidence of cardiogenic shock, pulmonary congestion and need for resuscitation as assessed by the ambulance doctor was similar in both groups. Angiography was performed before hospital discharge in 31 of 40 patients in group A and in 30 of 38 patients in group B. Angiography was not performed in 17 patients because of death before discharge (n=3), refusal by the patient (n=4), a wrong diagnosis (n=1), and logistic difficulties in studying patients from other cities (n=9).

Time intervals: The time from onset of chest pain until the ambulance was called was as short as 52 and 63 minutes in group A and group B, respectively, and did not differ significantly between the groups (Table II). Urokinase was administered to group A patients an average of 33 minutes later. In group B, however, thrombolytic therapy was delayed by an additional 43 minutes. As a result of the time gained by prehospital

thrombolysis, urokinase was administered >2 hours after symptom onset in only 4 of 40 patients (10%) in group A vs 20 of 38 (53%) in group B (Figure 2). The mean time to treatment was 85 ± 51 minutes in group A and 137 ± 50 minutes in group B ($p < 0.0005$).

Angiographic data and creatine kinase: The patency rate in the infarct-related artery prehospital discharge was 61% in group A and 67% in group B, and was similar in anterior and inferior AMI. Neither maximum creatine kinase nor left ventricular function differed significantly between groups A and B (Figure 3).

To evaluate the effect of thrombolytic therapy, patients with a patent infarct vessel were compared with patients in whom the infarct vessel was occluded at discharge. As evident from Figure 4, the left ventricular ejection fraction was significantly higher in patients with patent infarct vessels ($55 \pm 10\%$) than in patients with occluded vessels ($47 \pm 14\%$, $p = 0.025$). Hypokinesia at the infarct site averaged -2.0 ± 1.1 standard deviation in patients with a patent vessel and $-2.7 \pm$

FIGURE 2. Number of patients who received thrombolytic therapy within 1 hour, between 1 and 2 hours, between 2 and 3 hours, and between 3 and 4 hours after symptom onset, respectively.

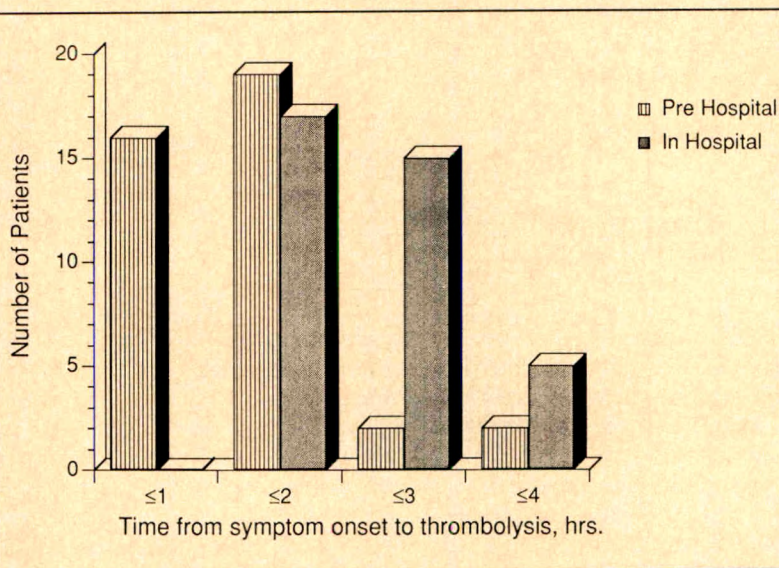


FIGURE 3. Comparison of the maximal creatine kinase (CK), left ventricular (LV) ejection fraction (EF) and wall motion at the infarct site between the prehospital and the in-hospital group. The differences were not statistically significant (n.s.). SD = standard deviation from the normal mean.

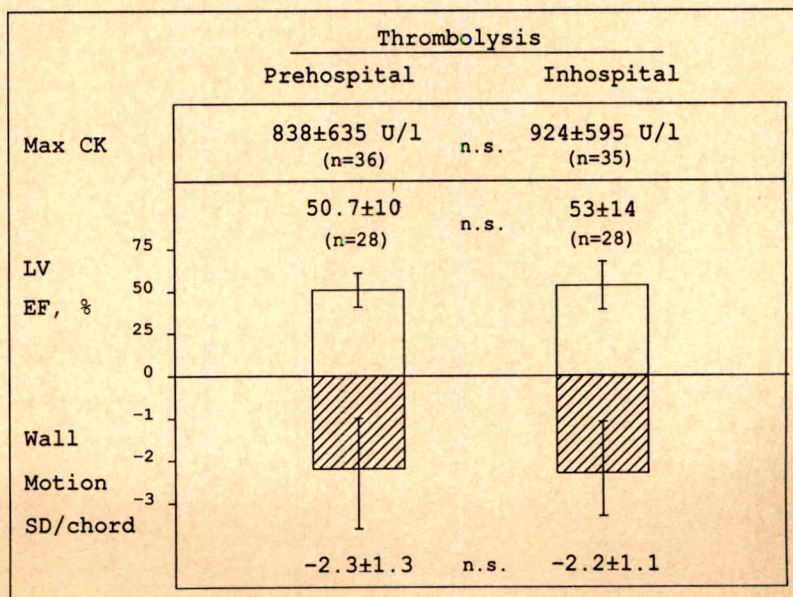


TABLE III Complications in the Prehospital Period

	Prehospital Group (n = 40)	In-Hospital Group (n = 38)
Drop in blood pressure (<90 mm Hg systemic or $\Delta p > 30$ mm Hg)	4	4
Ventricular fibrillation	2	1
Intubation	1	1
Cardiac massage	0	1
Bleeding complications	0	0
Wrong diagnosis	1	0
Death	0	0

TABLE IV Complications During Hospitalization

	Prehospital Group (n = 40)	In-Hospital Group (n = 38)
Ventricular tachycardia	8	6
Ventricular fibrillation	4	1
Bradycardia (<40/min)	3	5
Pulmonary congestion	8	8
Bleeding complications		
Puncture site	1	1
Hematuria	0	0
Gastrointestinal	0	1
Cerebral	0	0
Postinfarct angina	2	2
Reinfarction	4	5
Death	1	2
PTCA/CABG	4/1	1/0

CABG = coronary artery bypass surgery; PTCA = percutaneous transluminal coronary angioplasty.

1.1 SD in patients with an occluded vessel ($p < 0.02$). These data suggest that reperfusion resulted in a significant preservation of left ventricular function.

Stress test before discharge: Submaximal bicycle exercise testing, using the Bruce protocol,⁸ yielded similar results in both groups: The average maximal work load was 93 ± 30 W in group A and 82 ± 30 W in group B, and the maximal heart rate 119 ± 15 beats/

min in group A, 123 ± 20 beats/min in group B. The stress test was terminated because of dyspnea in 6 group B patients and 1 group A patient, angina pectoris in 2 group A patients, and significant ST-segment depression in 2 group A patients and 1 group B patient.

Complications: Complications during the prehospital phase were equally distributed between the 2 groups (Table III).

During the hospital phase (Table IV) 3 patients died (1 in group A and 2 in group B) from reinfarction 7 to 14 days after admission. Ventricular fibrillation tended to occur more often in group A than in group B patients (4 of 40 vs 1 of 38, respectively, difference not significant). Bleeding complications were rare, and no transfusions were necessary. One group B patient had gross hematuria due to oral anticoagulation.

DISCUSSION

In an earlier study we demonstrated that the time from onset of symptoms to thrombolytic therapy is a major determinant of myocardial salvage in patients with AMI.²

Thrombolytic therapy initiated <2 hours after the onset of symptoms improved regional left ventricular function and reduced infarct size more than therapy delayed by 3 to 5 hours. To further shorten the time to thrombolysis, some investigators advocate administering thrombolytic agents in the mobile care unit.^{4,5} Koren et al⁴ found significantly better left ventricular function and a lower QRS score and left ventricular end-diastolic pressure in a small group of patients treated in the mobile care unit than in patients treated in the hospital. The data of Martens et al⁵ suggest that patients treated in a mobile care unit have a higher reperfusion rate than patients treated after hospital admission. These clinical data indicate a possible role for initiating emergency treatment of AMI with streptokinase in the patient's home. Because controlled studies addressing this important question were lacking, we performed a randomized double-blind trial to study the benefit and risk

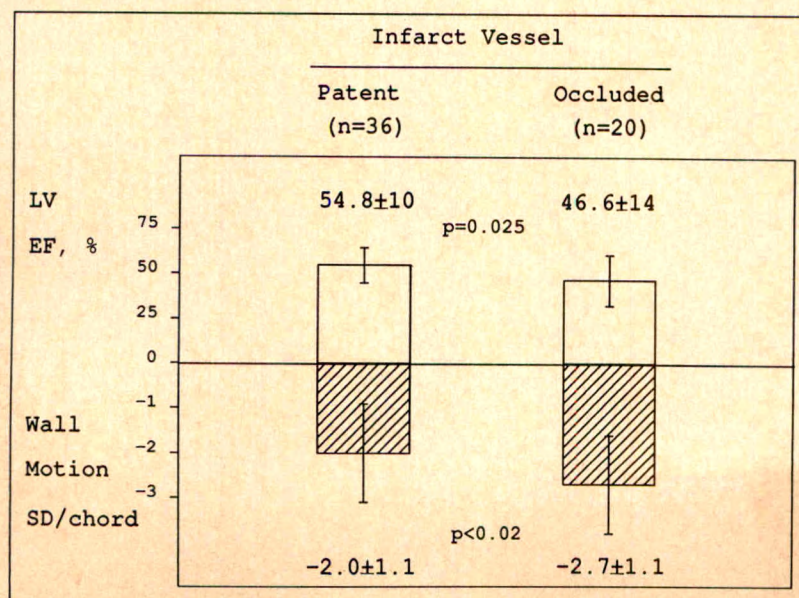


FIGURE 4. Comparison of left ventricular (LV) ejection fraction (EF) and wall motion at the infarct site between patients with a patent versus occluded infarct vessel at discharge. SD = standard deviation.

of prehospital thrombolysis in patients with AMI. Urokinase was selected as the thrombolytic agent because it was shown in a previous study to be effective when given as a bolus injection of 2 million units.⁹ Hypotension, known to be present after rapid intravenous infusion of streptokinase,¹⁰ is not observed after administration of an intravenous bolus of urokinase.

Time gained by prehospital thrombolysis: The mean time interval between onset of symptoms and prehospital administration of urokinase was 85 minutes, indicating that the patients studied were in a very early stage of AMI. Thrombolytic therapy within this time limit would be expected to be particularly effective in salvaging myocardium. The time gained by prehospital thrombolysis was 45 minutes, which is comparable to that of Koren et al⁴ (42 minutes) and Bippus et al¹¹ (46 minutes), although the patients of Koren were treated in the mobile care unit on the way to the hospital. Considering that 90% of patients in the prehospital group but only 46% of patients in the in-hospital group received thrombolytic therapy within the first 2 hours of their MI, a significant difference in infarct size would be expected in the former group. This, however, was not the case in the present study.

There are several factors that may explain these findings. First, the time saved by prehospital therapy, 43 minutes, included 29 minutes to transport the patient to the hospital and only 14 minutes to reconfirm the diagnosis, reassess the inclusion and exclusion criteria, and administer ampule B. Since the time from hospital admission to thrombolytic therapy is usually 45 minutes in the hospitals involved in the present study, this time interval in the present study was unusually short, and undoubtedly underestimates the time savings that could be expected.

Second, as a result of the rapid in-hospital therapy, there was a large overlap in time to treatment between the patients randomized to prehospital versus in-hospital therapy. In contrast, in an earlier study,² a fixed cut point of 2 hours was applied empirically to divide the patients into early versus late treatment groups. Koren et al⁴ also applied a fixed cut point, 1.5 hours, which is presumably empirical. This approach to data analysis is less robust statistically than the randomized, double-blind design used in the present study.¹²

Third, because pretreatment angiography was not performed, patients with subtotal occlusions could not be excluded. Previous studies show that up to 20% of patients presenting with AMI and meeting the entry criteria of the present study have subtotal occlusions, and that left ventricular function subsequently improves whether or not they receive thrombolytic therapy.¹³ Also, because only late patency was determined, the data of unsuccessfully treated patients further diluted the results.

Fourth, because of the rapidity with which in-hospital therapy was initiated, the range of time to treatment was narrow (<3 hours in >91% of the study group). This also tended to reduce sensitivity for detecting a relation between ventricular function and time.

Complications: Although no beneficial effect of prehospital thrombolysis on myocardial salvage could be

demonstrated in the present study, our data indicate that prehospital thrombolysis is safe and promising enough to warrant further study. Only 1 patient was misdiagnosed and treated by the ambulance doctor; he had a pulmonary embolism. Complications in the prehospital phase were rare in both groups. In particular, the urokinase bolus did not cause hypotension and reperfusion did not increase the incidence of life-threatening arrhythmias.¹⁴ No bleeding complications occurred in the prehospital phase and the in-hospital bleeding rate was comparable to that of thrombolysis with urokinase in another controlled trial.¹⁵ The reinfarction rate was 10 and 13% in groups A and B, respectively. The overall in-hospital mortality rate was very low, 3.8%. All patients who died 7 to 14 days after the acute infarction had reinfarction; in no patient was death the direct consequence of prehospital or in-hospital thrombolysis.

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Acute Myocardial Infarction and Chest Pain Syndromes After Cocaine Use

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Seventy patients hospitalized with chest pain after cocaine use were retrospectively evaluated to define the risk and clinical course of acute myocardial infarction (AMI). AMI developed in 22 patients (31%) and transient myocardial ischemia was seen in an additional 9 patients (13%). Coronary risk factors did not distinguish those who developed AMI from those who did not. The presenting electrocardiogram was abnormal in 20 of 22 patients who evolved AMI and in 19 of 48 of those who did not. Creatine kinase levels were elevated in 75% of the patients, including 65% of those who did not develop AMI, but creatine kinase-MB elevations were only observed in the AMI group. The route of cocaine administration did not predict AMI and there was no predilection for a particular coronary vascular bed. The length of time between drug use and onset of AMI pain was often quite prolonged (median interval, 18 vs 1 hour in the non-AMI group). Eight of the patients with AMI underwent cardiac catheterization and 4 had significant coronary narrowing.

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It is estimated that 30 million Americans have used cocaine at least once. Of these, 6 million use cocaine regularly and 1 million are compulsive users. Furthermore, there are 5,000 new users daily.¹ In addition to the socioeconomic problems associated with cocaine addiction, its use has resulted in the occurrence of many serious disorders including hyperthermia, status epilepticus, cerebrovascular accidents, intestinal ischemia, respiratory arrest, cardiac arrhythmias and myocardial infarctions.² Currently, only case studies and small series of patients with acute myocardial infarction (AMI) attributed to cocaine use have been reported.³⁻²³ We reviewed the records of a larger cohort of patients presenting with chest pain after cocaine use to determine the characteristics of those who had AMI and to describe their clinical course.

METHODS

Using ICD-9 codes, a list of patients admitted to the Montefiore Medical Center and North Central Bronx Hospital with a history of chest pain and cocaine use between January 1985 and February 1989 was obtained. A second list of patients was generated by cross-referencing myocardial infarction and coronary artery disease with cocaine use. The medical charts of these patients were reviewed to obtain the following data: coronary risk factors, route of cocaine administration, time of chest pain after last cocaine use, electrocardiographic changes, peak creatine kinase, creatine kinase-MB fraction, stress tests and cardiac catheterization results.

Admission electrocardiographic abnormalities (inverted T waves, ST-segment depressions or elevations, or Q waves) were described as anterior if changes were present in leads V₁ to V₄, inferior if changes appeared in leads II, III and aVF, and lateral if changes were present in leads I, aVL, V₅ and V₆. Ischemia was defined as an electrocardiographic change that occurred with chest pain and improved with pain resolution. Creatine kinase-MB was absent in this group.

Myocardial infarction was defined by a characteristic increase in the creatine kinase-MB fraction in association with typical chest pain or abnormal electrocardiogram, or both. These criteria are similar to those used by other major cardiovascular studies.²⁴ Enzyme levels were measured every 8 hours for 24 hours and at least once daily thereafter until normal. Because of different calibration standards, creatine kinase-MB fractions >5% at Montefiore Medical Center and >3% at North Central Bronx Hospital are defined as abnormal. Cardiac catheterizations and exercise stress tests were performed and interpreted using standard protocols.^{25,26}

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Statistical differences between the means of continuous variables were analyzed using the unpaired Student's *t* test or, for skewed samples, the Wilcoxon rank-sum test. Categorical data were analyzed by chi-square tests with the Yates' correction or, when appropriate, Fisher's exact test. A probability of 0.05 was statistically significant.

RESULTS

Between January 1985 and February 1989, 75 admissions coded for chest pain and cocaine use were identified. Of these, 70 charts (93%) were available for review. The number of hospital admissions for both of these conditions increased continuously over this 4-year period, from 2 admissions for chest pain and 1 for AMI in 1985, to 36 for chest pain and 11 for AMI in 1988. The mean (\pm standard error of the mean [SEM]) age of all patients presenting with chest pain after cocaine use was 34 ± 9 years. There were 56 men (80%). Table I contrasts the demographic characteristics of the AMI and non-AMI (which includes 9 patients with ischemia) groups and Table II summarizes clinical features of the 22 patients who developed AMI. The mean (\pm SEM) age in the AMI group was 36 ± 10 years and was not significantly different from the non-AMI group (age 33 ± 9 years). Of the 22 patients with AMI, 21 were men (95%; $p < 0.06$ vs women). Thirty-five of 48 non-AMI patients (73%) were men ($p < 0.05$). No patient had > 2 coronary risk factors and there was no statistical difference in the incidence of risk factors noted between the AMI and non-AMI groups.

Of the entire group of 70 patients, 25 smoked cocaine (as crack), 24 used intranasal cocaine and 8 used intravenous cocaine. For 13 patients the route of admin-

TABLE I Clinical Characteristics

	AMI	Non-AMI	p Value
No. of pts.	22	48	—
Age (years)	36	33	NS
Male/female	21/1	35/13	0.06
Systemic hypertension	5	5	NS
Cigarette smoker	18	30	NS
Diabetes mellitus	2	0	NS
Serum total cholesterol (> 220 mg/dl)	0	0	—
Family history of CAD	1	0	NS
Creatine kinase (IU)	1249	243	< 0.001
Abnormal admission ECG	20	19	< 0.001
Time from drug use (hours)	18	1	< 0.12

Data contrast patients with chest pain after cocaine use who developed acute myocardial infarction (AMI) with those who did not (non-AMI).
CAD = coronary artery disease; ECG = electrocardiogram; NS = not significant.

istration was not recorded. No route of administration was associated with an increased incidence of AMI.

The median time (\pm SEM) for onset of chest pain after cocaine use was 18 ± 68 hours in the AMI group and 1 ± 30 hours in the non-AMI group ($p = 0.12$, Wilcoxon rank-sum test). The time before the occurrence of chest pain was not recorded for 5 patients, 1 in the AMI group and 4 in the non-AMI group. Evaluation of the admission electrocardiograms showed that all but 2 patients with AMI (91%) had abnormal admission electrocardiograms, whereas most of the patients (60%) in the non-AMI group had normal electrocardiograms ($p < 0.001$). Of the remaining 40%, 9 had ischemic changes.

Of the 22 patients with AMI, 11 had Q-wave and 11 non-Q-wave infarcts. The mean (\pm SEM) creatine kinase value was $1,249 \pm 1,520$ IU/liter in the AMI

TABLE II Patients with Acute Myocardial Infarction After Cocaine Use

Age (yr) & Sex	Site of Infarct	Time to Chest Pain (hours)	Route of Administration	Peak CK (IU)	Coronary Risk Factors
19 M	Anterior	—	—	600	CS
24 F	Anterior	24	Crack	173	CS
24 M	Lateral	24	Intranasal	1,257	—
27 M	Lateral	9	Crack	771	CS
27 M	Inferior	96	Intranasal	323	CS
28 M	Inferior	336	—	5,094	0
29 M	Anterior	3	Crack	522	0
31 M	Inferior	24	Crack	904	CS
31 M	Unclear	48	Crack	541	CS
33 M	Inferior	24	Intravenous	464	CS
34 M	Anterior	24	Intranasal	5,300	CS
38 M	Unclear	12	Intravenous	1,140	SH, CS
38 M	Anterior	—	—	537	DM, CS
39 M	Inferior	2	Crack	386	SH
40 M	Anterior	36	Intranasal	404	CS
40 M	Lateral	24	—	562	SH, CS
42 M	Anterior	1.5	Crack	408	CS
46 M	Anterior	1	Intranasal	2,880	CS
47 M	Anterior	0.5	Crack	190	SH, CS
49 M	Inferior	10	Intranasal	1,466	CS
52 M	Inferior	1	Intranasal	233	SH, CS
52 M	Anterior	2	Intranasal	3,462	DM, CS
Total	—	18 ± 68	—	$1,249 \pm 1,520$	—

Values are expressed as mean \pm standard error of the mean.

CK = creatine kinase; DM = diabetes mellitus; CS = cigarette smoker; SH = systemic hypertension; 0 = normal; — = not available.

group and 243 ± 296 IU/liter in the non-AMI group. The mean (\pm SEM) creatine kinase was $1,947 \pm 1,917$ IU/liter in patients with Q-wave infarcts and 551 ± 330 IU/liter in the non-Q-wave infarct group. None of the non-AMI patients had measurable creatine kinase-MB although the peak creatine kinase value was elevated in 31 patients (65%) in the non-MI group. The electrocardiographic localization of the site of infarct demonstrates that no one coronary artery distribution was affected more than another (Table II).

There was no clinical evidence of recurrent ischemia in the AMI group and there were no fatalities. One patient who had a previous cocaine-associated AMI developed congestive heart failure and had a left ventricular ejection fraction of $<50\%$ and 1 patient had nonsustained ventricular tachycardia.

Eight of the AMI patients underwent cardiac catheterization. Four had coronary stenoses $>70\%$: 1 in the left anterior descending artery, 1 in the right coronary artery, 1 in the obtuse marginal and 1 in both the left anterior descending and the right coronary arteries. Three patients had normal coronary arteries and 1 had an occlusive thrombus. The mean (\pm SEM) left ventricular ejection fraction was $55 \pm 16\%$. In the non-AMI group, 1 patient underwent cardiac catheterization and had normal coronary anatomy. Four patients underwent exercise stress tests (3 in the AMI group and 1 in the non-AMI group). All of these results were negative for ischemia.

DISCUSSION

Cocaine is an alkaloid derivative of a plant grown in Central and South America. The effects of the drug are modulated by its ability to decrease reuptake of norepinephrine and dopamine.²⁷ The former causes tachycardia, vasoconstriction and hypertension, whereas the latter causes hyperactivity, sexual excitement and addiction.²

During the last 2 decades cocaine has become more available and its usage has increased.^{2,27} The increase in hospital admissions documented in our study may reflect this trend or may reflect an increased awareness by health professionals of the medical complications of cocaine use. The first case report of myocardial infarction after cocaine use was published in 1982 and since that time there have been an additional 41 reported cases.³⁻²³

We evaluated a large cohort of patients presenting with chest pain after cocaine use. One-third of these developed AMI. This is the largest published experience of AMI after cocaine use and it allowed us the opportunity to contrast the clinical features of patients that did not have AMI with those that did.

In our series, men were 4 times more likely to develop chest pain after cocaine ingestion and 6 times more likely to develop AMI than women. Although this observation parallels the incidence of AMI in the general population,²⁸ it probably reflects a bias in our study population since men may have been more likely to use the drug. The average age of patients with AMI after cocaine use both in our study (36 years) and in previous

reports (31 years) was significantly lower than the mean age of patients with AMI in the general population,²⁸ again reflecting the population at risk.

Our data suggest that the initial electrocardiogram is the most sensitive predictor of who will develop AMI. However, because 2 patients who were admitted with normal electrocardiograms went on to develop AMI, a normal electrocardiogram alone does not preclude this diagnosis. Creatine kinase alone is not helpful since the mean peak creatine kinase value for patients who had chest pain but did not develop AMI was greater than twice normal. This has been previously described in cocaine users and is considered to reflect skeletal muscle injury due to seizures, hyperthermia or compression.²⁹ In our series there were equal numbers of Q-wave and non-Q-wave infarcts. In contrast to published reports, in which 60% of cases had anterior wall infarctions, we found no predilection for any vascular distribution.

Four of the 8 patients that underwent cardiac catheterization had significant coronary artery stenoses. This may represent a skewed population because only those suspected of having coronary artery disease may have been studied. Analysis of the 42 published case reports revealed 15 patients with normal coronary arteries, 10 with thrombus and 10 with significant coronary artery stenoses.³⁻²³ The benefits of catheterization or stress tests, or both, require further study before recommendations can be made, especially in light of the benign clinical course noted in these patients with AMI.

We also found that the likelihood of developing AMI after cocaine use was not affected by the route of administration, despite the fact that higher concentrations of cocaine are routinely attained after intravenous injection and smoking crack.² This suggests that AMI may not be due to primary effects of cocaine but rather to its secondary effects (i.e., on platelets, the coagulation cascade, the vascular endothelium, or a combination of these) leading to gradual thrombus formation.³⁰ This is supported by the fact that the median time to onset of chest pain after cocaine ingestion was longer in patients who developed AMI than in those who did not.

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Comparison of Thallium-201 and Technetium-99m Hexakis 2-Methoxyisobutyl Isonitrile Single-Photon Emission Computed Tomography for Estimating the Extent of Myocardial Ischemia And Infarction in Coronary Artery Disease

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Single-photon emission computed tomography (SPECT) using thallium-201 (Tl-201) was compared with technetium-99m hexakis 2-methoxyisobutyl isonitrile (Tc-99m MIBI) in 24 patients with coronary artery disease. Patients exercised to the same work load as each isotope was studied. Normal and hypoperfused left ventricular mass was determined with an automated method.

Estimated total left ventricular mass was similar for both stress/redistribution Tl-201 and stress/rest Tc-99m MIBI images. The mean estimated defect size in the redistribution Tl-201 images was 32 ± 34.7 vs 33 ± 38.4 g in the resting Tc-99m MIBI studies (difference not significant). The individual determinations of defect mass were highly correlated ($r = 0.93$; $p < 0.0001$). Estimated defect size in the stress Tl-201 images (52 ± 46.2 g) was significantly larger than the exercise Tc-99m MIBI estimates of defect mass (42 ± 39.9 g; $p < 0.05$). A linear correlation existed between stress thallium and technetium estimates of defect size ($r = 0.85$) but 15 of 24 Tc-99m MIBI defects were smaller than the Tl-201 defects. Partial redistribution of Tc-99m MIBI could explain the discordance.

Stress Tc-99m MIBI SPECT defect size determined by visual interpretation or by the use of isocount analysis may be smaller than what is seen with stress Tl-201 SPECT.

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Thallium-201 (Tl-201) myocardial scintigraphy is used frequently to detect the presence or absence of coronary artery disease^{1,2} and to predict the prognosis of patients with ischemic heart disease.³ Although Tl-201 imaging has enhanced the diagnostic abilities of clinicians, the isotope's slow myocardial clearance and long physical half-life limit the injected dose.

Recently, a number of technetium compounds have been evaluated as possible substitutes for Tl-201 as an imaging agent in patients with known or suspected ischemic heart disease.^{4,5} The isonitrile complexes have attracted considerable interest because they have a myocardial distribution that is flow dependent.⁶⁻⁸ In addition, technetium is inexpensive, is readily available and can be administered in doses that would allow improved image quality.⁹⁻¹⁶

If the isonitrile compounds are used as a substitute for Tl-201 in perfusion imaging, it would be useful to establish the equality of defect size between the 2 agents. Thus, we evaluated patients with known coronary artery disease using Tl-201 and technetium-99m 2-methoxyisobutyl isonitrile (Tc-99m MIBI) as myocardial imaging agents. Single-photon emission computed tomographic (SPECT) studies were obtained during exercise and after redistribution (or at rest). An automated computer algorithm was used to estimate total left ventricular mass and defect size in these patients' 2 isotope studies.

METHODS

Patient selection and exercise testing: Twenty-four patients were enrolled into this study (19 men and 5 women). Twenty-three patients had a documented prior myocardial infarction and 14 patients had undergone cardiac catheterization. A history of chronic stable angina was present in 20 patients. All patients gave their informed consent to a protocol approved by the Harbor-UCLA Medical Center Human Subjects Committee. Nine patients underwent a symptom-limited treadmill stress test using the Bruce protocol. The remaining patients exercised on an electronically braked upright bicycle with a work load commencing at 50 W and increasing 25 W every 3 minutes.

Patients exercised for an identical duration and to the same external work load during each stress test. The duration of the first test determined the duration of the second test. Three millicuries (mCi) of Tl-201 were injected during peak exercise, exercise was continued for an additional minute and imaging was begun within 5 minutes. Redistribution Tl-201 imaging was performed 3 to 4 hours after the initial stress imaging. During a separate study, 25 mCi of Tc-99m MIBI were injected during peak exercise through a peripheral vein and a 30-second first transit radionuclide angiogram was obtained but is not reported in this communication. Isonitrile perfusion imaging was performed 2 hours thereafter.¹⁷ A resting Tc-99m MIBI study was performed using the same amount of isotope on a separate day. Resting Tc-99m MIBI imaging was performed before the stress isonitrile study in 9 of the 24 patients. Thallium-201 stress imaging preceded the technetium stress studies in 12 of the 24 patients. The order of the imaging was based on the availability of Tc-99m MIBI. The same type of exercise (treadmill or bicycle) was used for both the Tl-201 and the Tc-99m MIBI stress studies in each individual patient. All antianginal medications were continued without changes during both isotope studies.

SPECT imaging: Studies were obtained on a large field-of-view rotating gamma camera (Technicare, Omega 500, Solon, Ohio) equipped with a parallel hole, general all-purpose collimator. The spectrometer was centered over the 80-keV emissions of Tl-201 with a 20% window. Technetium isonitrile studies were obtained with a window set to record the 140-keV emissions. Thirty-two matrixes were obtained during a 180° rotation from a left posterior oblique to a 30° right anterior oblique projection.¹⁸ Each 64 × 64 matrix was collected for 30 seconds during each of the 32 steps. Data processing was performed on a dedicated computer (Sopha SIMIS-5, Baltimore, Maryland) by means of a back projection algorithm with pure ramp filtering and no attenuation correction. Transaxial slices were then reconstructed and realigned into frontal and sagittal sections with the manufacturer's software. Only realigned slices cut perpendicular to the long axis of the left ventricle (short-axis slices) were used for analysis in this study. No background subtraction was performed.

Estimation of left ventricular mass and ischemic mass from SPECT: Estimated total left ventricular mass was determined using a method that has been validated in this laboratory in an animal model¹⁹ and in patient studies.^{20,21} The technique is capable of providing accurate estimates of left ventricular mass with a 5.9% mean absolute difference between a single Tl-201 stress and redistribution study pair and an average absolute difference of 7.2% when comparing the masses of 2 redistribution studies performed approximately 5 weeks apart. Areas of significant hypoperfusion were defined as volume elements within the computer-defined myocardium in each short-axis slice that fell below 45% of the maximal counts in the left ventricle. Our previous work¹⁹ with Tl-201 SPECT has demonstrated that infarction determined histologically and biochemi-

cally correlates well with estimates of infarct size derived with this technique. A defect detected by Tl-201 SPECT or Tc-99m imaging that represented <7 g of myocardial mass was considered within the normal range. (The smallest infarct we have imaged experimentally was 7 g in size.)

Total myocardial mass and defect mass were calculated by observers unaware of the patients' clinical findings.

Statistics: Regression analyses, correlation coefficients, as well as paired and unpaired *t* tests were performed using standard methods. Mean values are reported ± 1 standard deviation.

RESULTS

Exercise testing: Each patient exercised to the same work load and for the same duration during stress imaging with Tl-201 and Tc-99m MIBI. Maximal systolic blood pressures were similar (160 ± 30.9 and 168 ± 27.5 mm Hg; Tl-201 and Tc-99m MIBI, respectively; difference not significant). Maximal exercise heart rate (112 ± 15.8) during the Tl-201 studies was slightly, but significantly, lower than values noted during the Tc-99m MIBI stress studies (119 ± 19.3 beats/min; $71 \pm 11.5\%$ of predicted; $p < 0.001$). The maximal double product during the Tl-201 stress test was 179 ± 43.4 and was lower than the Tc-99m MIBI test value of 200 ± 44.0 ($p < 0.001$).

Because all patients had known coronary artery disease, antianginal medications were continued without change during the 2 stress studies. All patients were receiving β blockers or calcium antagonists, or both, at the time of the stress studies (13 of 24 received β blockers; 15 of 24 took calcium antagonists).

Image characteristics: The mean maximum pixel count in the left ventricular region of interest was 903 ± 351 counts (range 342 to 1,883) for the stress Tc-99m MIBI studies. This value was 4.8 times higher than the value recorded from the Tl-201 images (189 ± 62 ; range 102 to 340 counts/pixel; $p < 0.001$).

Maximal image counts averaged 740 ± 306 (range 214 to 1,585 counts/pixel) in the resting Tc-99m MIBI studies and 117 ± 33 (range 72 to 196) in the redistribution Tl-201 studies. The 6.3-fold difference was significant ($p < 0.001$).

A significant ($p < 0.001$) but weak correlation ($r = 0.647$) was noted when the maximal counts from the stress thallium and isonitrile studies were compared. A similar relation ($p < 0.005$; $r = 0.563$) was noted when the maximal counts in the redistribution Tl-201 and resting Tc-99m MIBI images were evaluated.

Estimates of left ventricular mass: Estimated total left ventricular mass during the stress Tl-201 study correlated well with that of the exercise Tc-99m MIBI study ($r = 0.91$; standard error of the estimate [SEE] = 18.9; $p < 0.001$; Table I). Left ventricular mass estimated from the redistribution Tl-201 study was similar to the value obtained from the analysis of the resting technetium-99m study ($r = 0.89$; SEE = 22.6; $p < 0.001$). The correlation coefficient for comparing total left ventricular mass estimated from the stress Tl-201 study

TABLE I Estimates of Left Ventricular Mass

	Stress	Redistribution/ Rest
Mean Tl-201 SPECT left ventricular mass (g)	242 ± 50	237 ± 54
Mean Tc-99m MIBI SPECT left ventricular mass (g)	232 ± 43	233 ± 47
Mean absolute difference (g)	14 ± 18 (5.8%)	18 ± 17 (7.6%)

SPECT = single-photon emission computed tomographic; Tc-99m MIBI = technetium-99m hexakis 2-methoxyisobutyl isonitrile; Tl-201 = thallium-201.

versus the redistribution Tl-201 study was $r = 0.94$; $SEE = 19.9$; $p < 0.001$). A comparison of total mass estimates based on the stress versus the resting Tc-99m MIBI studies yielded a correlation coefficient of $r = 0.91$ ($SEE = 20.7$; $p < 0.001$).

Estimates of defect mass: The mean estimated defect or hypoperfused mass noted on the stress Tl-201 studies was 52 ± 46.2 g. Defect mass estimated from the stress Tc-99m isonitrile studies was 19% smaller (42 ± 39.9 g; $p < 0.05$). The estimates of defect size using the 2 isotopes were significantly correlated ($r = 0.85$; $SEE = 6.6$; $p < 0.0001$; Figure 1). However, the linear regression between the 2 isotopes yielded a slope of 0.74 (Figure 1) and the defect size was smaller in 15 of 24 of the Tc-99m MIBI studies. Altering the isocount value used to determine Tc-99m MIBI defect size did not correct the discrepancies in estimated defect mass. Typical

examples of images obtained with the 2 isotopes are shown in Figures 2 to 4.

Defect mass estimated from the redistribution Tl-201 study was 32 ± 34.7 g, and was 33 ± 38.4 g based on the resting isonitrile study. These estimates of defect mass were closely correlated with $r = 0.93$ ($SEE = 4.0$; $p < 0.0001$; Figure 5). Five of the rest-redistribution pairs had defect masses small enough to be considered normal variants.

DISCUSSION

Study design: In this study we attempted to compare stress and rest/redistribution imaging with Tl-201 and Tc-99m MIBI as closely as possible. Patients were receiving the same medications during each study and exercised for identical periods of time using an identical exercise protocol. We deliberately studied patients who had known coronary artery disease (by virtue of a previous myocardial infarction or prior coronary arteriography) to assess the ability of the 2 isotope studies to detect the presence and extent of ischemia or scar.

Evaluation of counting statistics: The results of this investigation are consistent with previous reports that have demonstrated substantially higher counting rates when Tc-99m MIBI is substituted for Tl-201 as a myocardial perfusion agent.^{9-11,13} Maximum count activity in the stress Tc-99m MIBI study was 4.8 times higher than that obtained from corresponding Tl-201 stress images. Likewise, maximal image counts averaged 740 counts/pixel when resting Tc-99m MIBI was compared with redistribution Tl-201 imaging (117 counts/pixel; 6.3-fold difference). The magnitude of the difference in

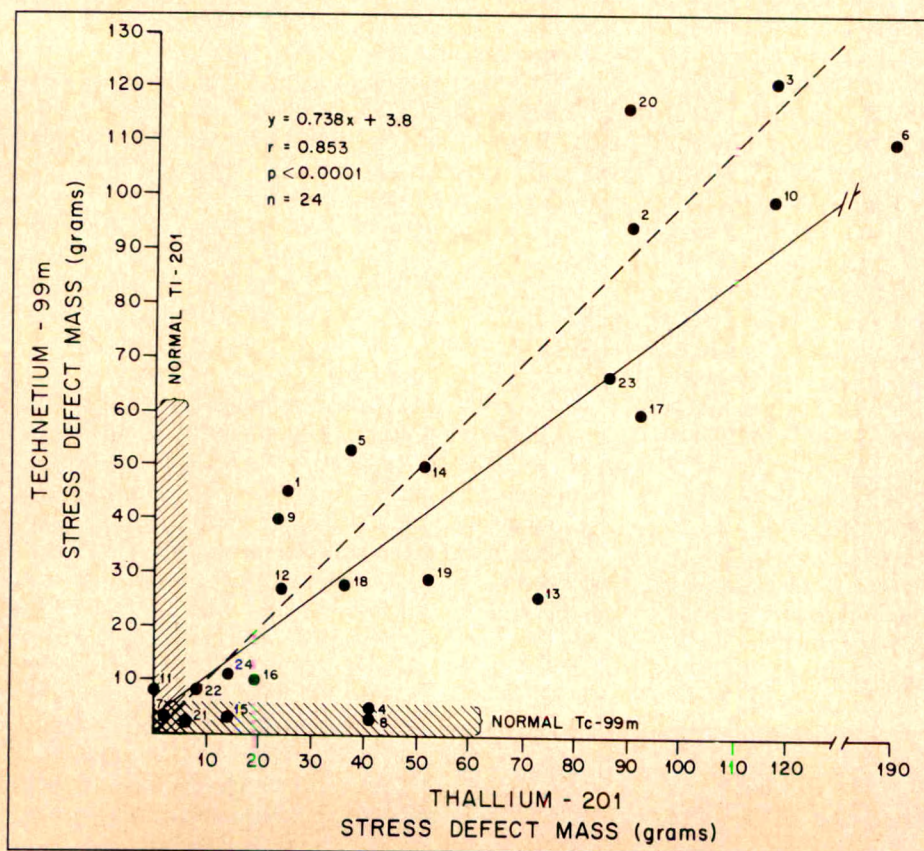


FIGURE 1. Thallium-201 (Tl-201) single-photon emission computed tomographic (SPECT) defect mass during stress is plotted on the horizontal axis. Technetium-99m (Tc-99m) isonitrile SPECT defect mass during stress is plotted on the vertical axis. The lower limit of defect detection (7 g) is depicted by a diagonal grid. Solid line represents the regression equation generated from these data. Dashed line is the line of identity. The stress Tc-99m isonitrile SPECT defects tend to be smaller than their corresponding Tl-201 SPECT defects.

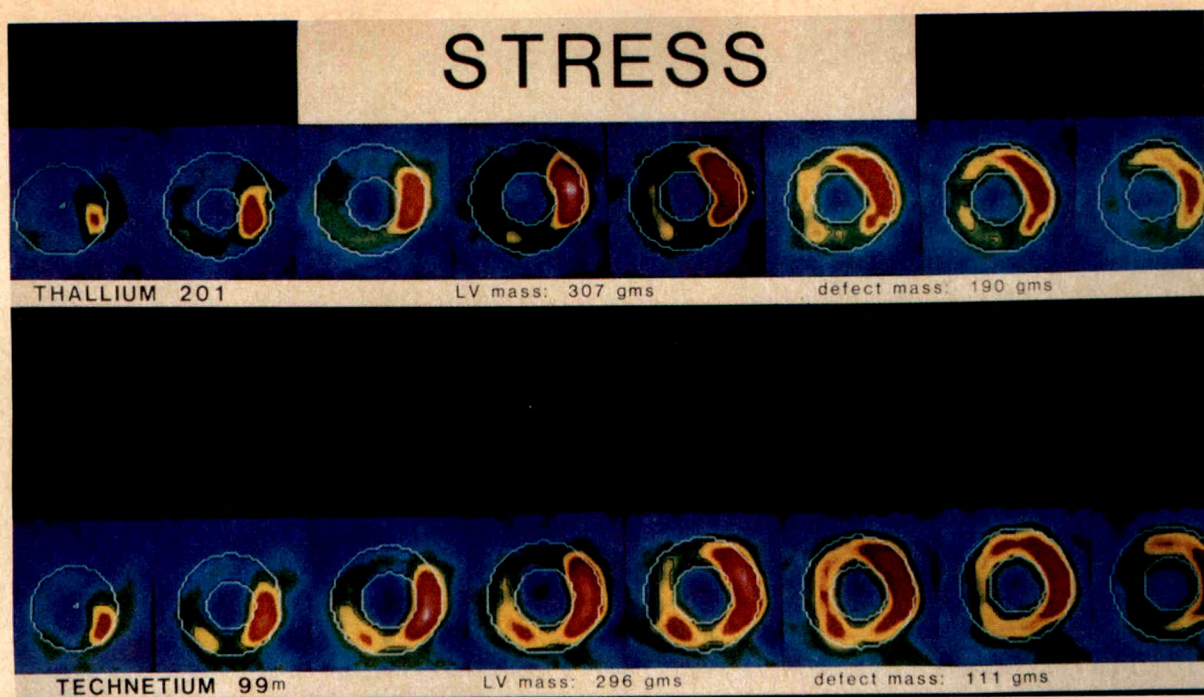


FIGURE 2. A typical thallium-201/technetium-99m isonitrile stress pair is depicted. The color scale for isotope activity is on the left with white indicating the greatest activity and blue the least. White circles represent the computer-generated estimates of the epicardial and endocardial borders. Hypoperfusion was defined by a 45% isocount line roughly where the yellow color makes a transition to green. In this example the left ventricular (LV) mass estimates from both isotope studies are comparable. However, the defect mass derived from thallium-201 imaging (190 g) is substantially larger than that detected by the technetium isonitrile (111 g). The inferior defect is appreciably larger in the thallium image on the first 7 "short-axis" slices. The greater extent of the anterior defect is apparent on slices 5 to 7 (from left to right).

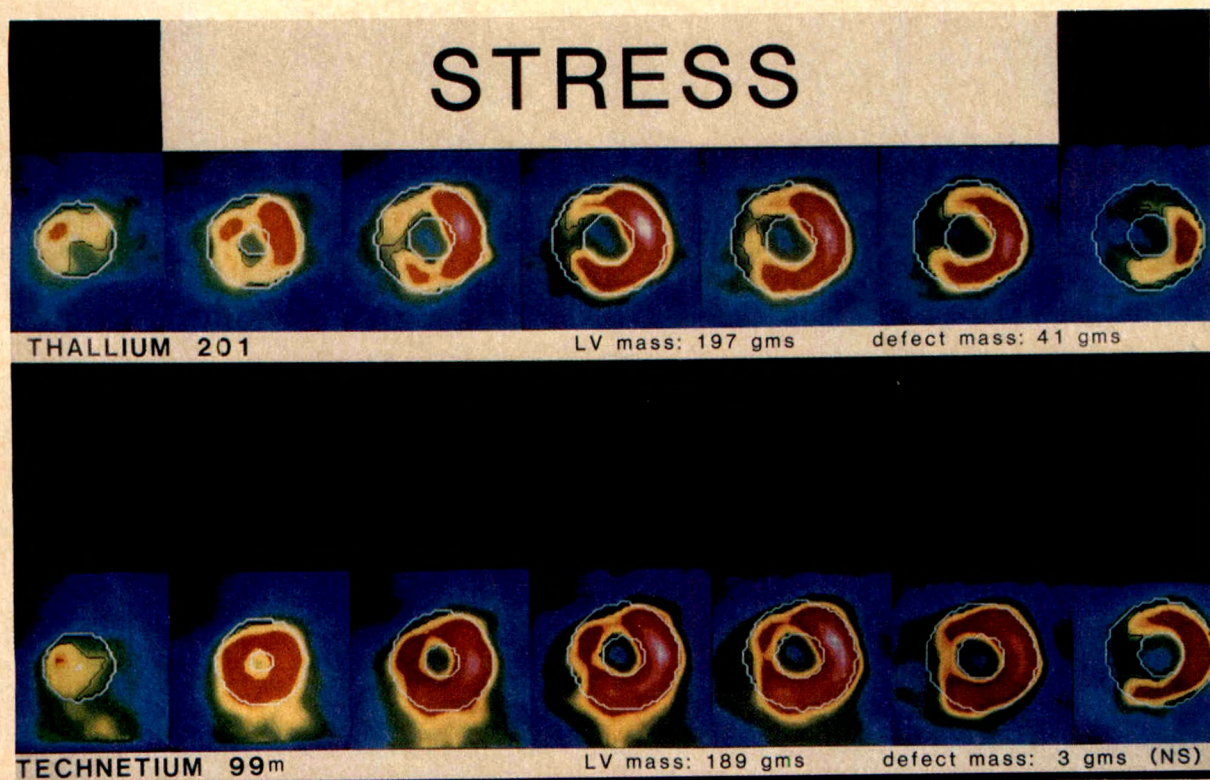


FIGURE 3. A stress thallium-201/technetium-99m isonitrile pair is depicted. Explanations as in Figure 2. The left ventricular (LV) mass algorithm provides similar measures of total mass. A defect estimated to be 41 g in total weight is noted on slices 1 to 6 on the stress thallium-201 images. Using the same definitions for hypoperfusion on the technetium images yields a defect mass of 3 grams which is not significant. No transmural defects are present on the technetium images as opposed to the thallium-201 image. NS = not significant.

REDISTRIBUTION / REST

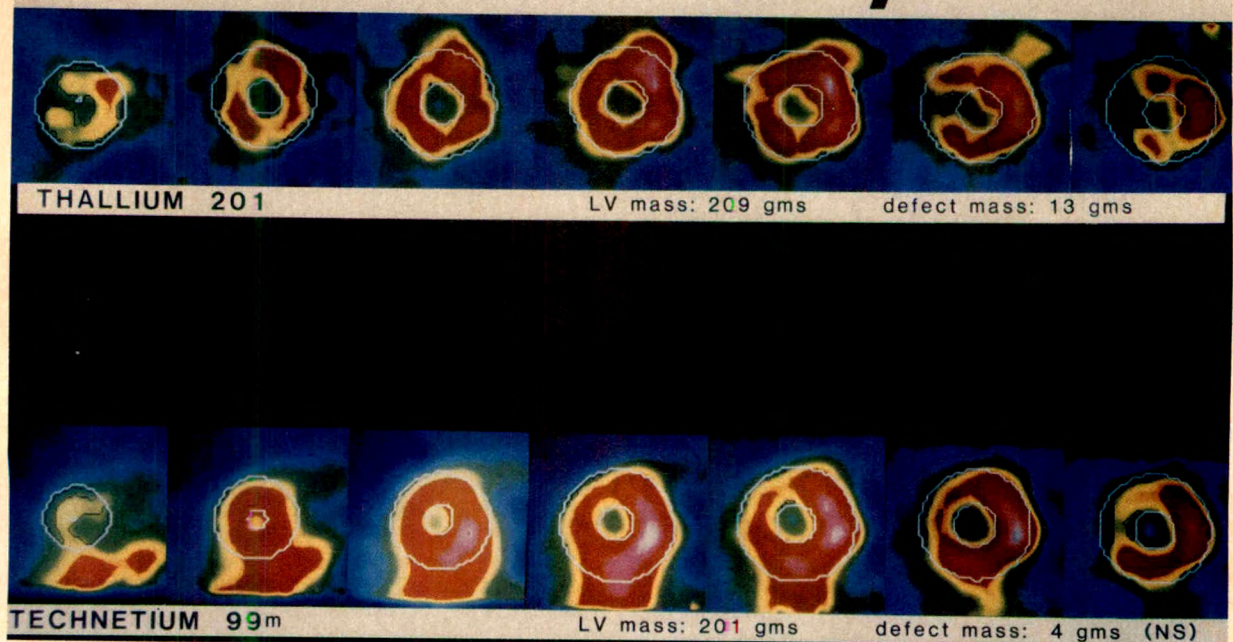


FIGURE 4. A redistribution thallium image and a resting technetium image from the same patient as Figure 3 is presented. Explanations as in Figure 2. Close concordance in the redistribution/resting left ventricular (LV) mass is apparent in this pair as well as in the corresponding stress pair shown in Figure 3. Despite the large amount of subdiaphragmatic technetium-99m activity present in this study, the left ventricular mass algorithm provides a total mass estimate which is similar to that obtained from the thallium-201 image. Defect mass from the thallium image is estimated to be 13 g, almost all of which is present in slice no. 6 of the thallium image. NS = not significant.

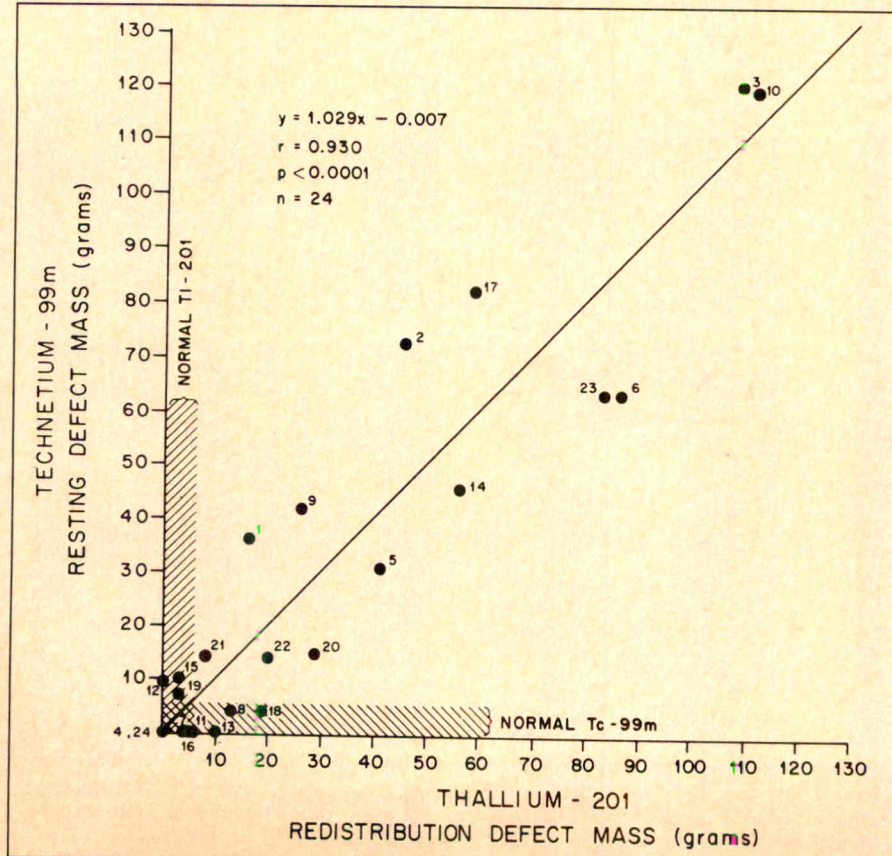


FIGURE 5. The redistribution defect mass determined from thallium-201 (Tl-201) single-photon emission computed tomography and technetium-99m (Tc-99m) isonitrile are displayed as in Figure 1.

count rate was consistent with the ratio of the injected doses of Tl-201 (3 mCi, 111 MBq) and Tc-99m MIBI (25 mCi, 925 MBq).

Estimates of total left ventricular mass: Total left ventricular mass estimated from the stress Tl-201 studies was not significantly different when compared with mass estimates from the redistribution images (Table I). We did not alter the reconstruction algorithm or our method for determining left ventricular mass when analyzing the Tc-99m MIBI tomographic studies. Nonetheless, estimates of left ventricular mass obtained from the isonitrile images did not differ significantly from the values obtained from the Tl-201 studies.

Estimates of defect size: No significant difference in estimated defect size was seen when the redistribution Tl-201 and resting Tc-99m MIBI studies were compared (Figure 5). In fact, estimated mean defect mass was virtually identical when data from the Tl-201 SPECT study (32 ± 34.7 g) were compared with data from the Tc-99m MIBI SPECT study (33 ± 38.4 g). Estimated defect masses from the rest/redistribution studies were correlated with an r value of 0.93 ($p < 0.0001$). This close relation between Tl-201 and Tc-99m MIBI defect size was found despite a 6.3-fold difference in maximal counts in the respective images and the use of a method for defining normal and abnormal mass that was created for Tl-201 imaging.

The concordance in defect size noted between the redistribution Tl-201 and resting Tc-99m MIBI studies was not present when stress images were evaluated. Although a linear correlation was found ($r = 0.85$), the slope of the regression line was 0.74 (Figure 1), reflecting smaller defects in the stress Tc-99m MIBI studies ($p < 0.05$).

Possible explanations for these results: Although the mean heart rate, blood pressure and double product at maximal exercise were similar during the 2 stress perfusion studies, individual variations may be responsible for the differences in defect size. However, no consistent changes in any of the exercise parameters correlated with the differences in defect size. In fact, the exercise heart rates and double products during the isonitrile stress studies were slightly but significantly higher than those noted in the Tl-201 studies—a finding opposite what would be expected because of the smaller stress Tc-99m MIBI defects.

We used a SPECT reconstruction and a left ventricular mass processing routine designed for Tl-201 SPECT studies. The substantial differences in imaging properties between Tl-201 and Tc-99m MIBI may necessitate unique reconstruction techniques such as different filtering. However, in this investigation results from redistribution Tl-201 imaging mirrored data obtained from the resting Tc-99m MIBI studies. Thus, for rest/redistribution imaging, the methods we used for determining left ventricular mass and left ventricular defect size appear to be appropriate for both isotopes.

The higher counting rates noted in the exercise Tc-99m MIBI studies may allow for more "shine through" or a "blooming effect," which could result in smaller image defects. However, the average maximum stress

Tc-99m MIBI count rate (903 counts/pixel) was only 22% higher than the maximal image counts found in the resting Tc-99m MIBI studies that had defect sizes similar to the redistribution Tl-201 images. Further investigation with a lower dose of Tc-99m MIBI or using a high resolution collimator would be necessary to address these possibilities. The use of different isocount values did not alter the discrepancy in stress defect size.

Possible effects of antianginal agents and ischemia:

All patients in this study were receiving β or calcium blockers, or both. Therapy with antiischemic agents is known to alter the sensitivity of thallium-201 imaging for detecting coronary artery disease.^{21,22} Conceivably, exercise Tc-99m MIBI uptake differs from Tl-201 in the presence of β blockers or calcium antagonists. Alternatively, because metabolic changes²³ and hypoxia²⁴ have different effects on Tl-201 and Tc-99m MIBI kinetics, the larger thallium defects may represent a true difference in myocardial integrity during ischemia.

Another possible explanation for our results is the observation by Leppo and Meerdink²⁵ that net myocardial extraction of Tl-201 is significantly different from Tc-99m MIBI in the isolated perfused rabbit heart. In addition, a recent report²⁶ suggests that myocardial redistribution of Tc-99m MIBI occurs after transient ischemia. If the latter observation is verified, the 2-hour delay between the injection of Tc-99m MIBI and image acquisition in this investigation may explain the disparity in stress defect size. Thus, the observations in this study may reflect actual differences in isotope kinetics during or subsequent to exercise. These possibilities were not anticipated in this investigation and will require further study.

Limitations of the SPECT quantitation: The SPECT images in this investigation were ungated and motion artifacts were likely present. In addition, the limited resolution of the imaging system²⁷⁻²⁹ and the lack of attenuation correction will prevent the SPECT images from mirroring the precise pathologic anatomy of the left ventricle.³⁰ Also, the SPECT left ventricular mass determination makes assumptions similar to those used in the contrast angiographic determination of mass, e.g., a relatively uniform wall thickness. Despite these inherent limitations, the left ventricular mass algorithm is accurate in an animal model¹⁹ and highly reproducible in both animals and humans.¹⁹⁻²¹

Other investigators have found that specific quantitative analysis routines are necessary when analyzing planar Tc-99m MIBI studies.³¹ Our method for analyzing SPECT images is based on the identification of the left ventricular endocardial and epicardial surfaces with a superimposed isocount profile to define hypoperfusion. Thus, it differs from other quantitative analysis methods that have been described. It is analogous to a visual interpretation of tomographic images. In this study, the differences in computer-defined defect size corresponded to what can be observed visually (Figures 2 to 4). Thus, the results of Tc-99m MIBI imaging performed 2 hours after stress may underestimate the extent of ischemia when compared with Tl-201 imaging obtained immediately after exercise.

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Recanalization of Chronic Total Coronary Arterial Occlusions by Percutaneous Excimer-Laser and Laser-Assisted Angioplasty

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A low primary success and high restenosis rate after recanalization of chronic total occlusions by conventional coronary angioplasty have encouraged the application of new interventional techniques like excimer-laser angioplasty. In 39 patients with a coronary occlusion for 1 to 12 months, recanalization was attempted by laser angioplasty through a multifiber-catheter coupled to a pulsed XeCl excimer laser. After successful passage of the occlusion by a standard guidewire in 27 patients (69%), the laser catheter was advanced over the central guidewire and crossed the occlusion in 25 patients (64%). In 2 patients with unsuccessful passage of the laser catheter, the subsequent attempt with a low profile balloon catheter also failed. In 19 of the 25 patients with successful laser recanalization, the residual stenosis exceeded 50% and was therefore followed by additional balloon angioplasty. The average residual stenosis after laser was $61 \pm 17\%$ of the vessel diameter, and after balloon angioplasty $28 \pm 9\%$ ($n = 19$), whereas after laser angioplasty alone it was $38 \pm 5\%$ ($n = 6$). No complications associated with the laser application were observed. Angiographic control after 24 hours showed a reocclusion of 2 (8%) recanalized vessels.

In this pilot study, laser angioplasty proved to be a safe and feasible method for the treatment of chronic total coronary occlusions. Because it was necessary to guide the catheter by a central wire, the primary success was limited by a successful passage of the wire of the occlusion. The rate of stand-alone laser angioplasty has to be increased by future improvements of the technique to enable a comparative evaluation of this method with conventional angioplasty.

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Percutaneous transluminal coronary angioplasty is the standard technique for the nonsurgical treatment of symptomatic coronary artery disease.¹ Whereas the advances in balloon technologies have increased the immediate success rate, the long-term outcome is limited by the high rate of restenosis.^{2,3} This is still more discouraging for the treatment of chronic total coronary occlusions.⁴⁻⁸

The laser devices currently under clinical investigation to improve the outcome of angioplasty bear the potential of ablating atherosclerotic plaques. While the thermal laser probes cause considerable damage to the vessel wall when applied in coronary arteries,⁹ the pulsed energy delivered by excimer laser sources ablates with minor damage to the adjacent tissue.¹⁰⁻¹² This might be advantageous in the treatment of coronary artery disease because it would avoid possible causes of restenosis like mechanical distension and dissection after balloon angioplasty. Even if additional balloon angioplasty were required, the initial recanalization and reduction of plaque material by laser might have a favorable impact on the incidence of restenosis. The guidance of the laser catheter over a wire and the principle of laser ablation on contact with the adjacent tissue reduced the danger of perforation. After successful application of excimer laser angioplasty in peripheral arteries,^{13,14} it was recently used in coronary arteries.^{15,16} The present study was undertaken to assess the safety, feasibility and primary success of percutaneous excimer laser angioplasty in patients with chronic total coronary occlusions.

METHODS

Laser source and catheter system: An XeCl-excimer laser source (MAX 10, Fa. Technolas, Graefelfing, Federal Republic of Germany) emitted pulsed laser energy of 50 to 120 mJ/pulse at a wave length of 308 nm and a pulse width of 55 to 60 ns. The pulse repetition during angioplasty was adjusted to 15 or 20 MHz. Laser catheters of various sizes from 4 to 5.5Fr outer diameter were available. They were of a similar concentric design with a central lumen for a 14/1,000-inch guidewire to avoid perforation of the vessel wall during the advancement of the laser catheter. The laser energy was transmitted by a ring of 18 (4Fr catheter), 28 (5Fr) or 33 (5.5Fr) quartz fibers (100- μ m diameter) (Fa. Technolas, Graefelfing, Federal Republic of Germany). Technical details of the catheter system are summarized in Table I.

TABLE I Technical Data of the Laser Source and Catheter System

Wave length	308-nm (XeCl)
Pulse energy	50–120 mJ
Pulse width	55–60 ns
Repetition rate	2–40 Hz
Energy fluency/fiber surface area	
4Fr catheter	32–46 mJ/mm ²
5Fr catheter	45–59 mJ/mm ²
5.5Fr catheter	54–69 mJ/mm ²

Before inserting the laser catheter into the guiding catheter, the transmitted energy was adjusted with a power meter. The energy output of the laser source was tuned to get about 80% of the maximum output specific for each catheter size, according to prior in vitro tests. These tests had shown no significant loss of energy transmittance at this energy level during 5,000 pulses at a pulse rate of 20 Hz.

Procedure: All patients had undergone a diagnostic angiography at our catheterization laboratory or in a referring cardiac rehabilitation center. A 9Fr giant lumen guiding catheter (Interventional Medical, Danvers, Massachusetts) was inserted through a femoral sheath. A rigid standard guidewire (ACS, Santa Clara, California) was tried to pass the occlusion. If the guidewire caused a dissection or could not be advanced far enough downstream into the distal vessel segment, the procedure was terminated.

When the guidewire had passed the occlusion, the laser catheter with a radiopaque marker at the tip was introduced into the occluded vessel. The laser procedure was then begun for 20 to 30 seconds, while advancing the catheter slowly with gentle force to ensure contact of the catheter tip with the tissue. Energy delivery was repeated until the laser catheter crossed the occlusion. When the occlusion had been passed, the catheter was drawn back and advanced slowly through the occlusion 2 to 3 times with the laser switched on. The progress during laser angioplasty was constantly controlled by fluoroscopy. The procedure was terminated when there was opacification of the downstream vessel segments by contrast medium injected through the guiding catheter while the laser catheter was still within the recanalized segment. After laser angioplasty, a control angiogram of orthogonal views was recorded. If the residual stenosis were >50% of the pre- and poststenotic vessel diameter, additional balloon dilatation was done. After 24 hours a control angiogram was obtained.

Patients: Percutaneous coronary excimer laser angioplasty was attempted in 39 consecutive patients (33 men and 6 women, age range 36 to 78 years [mean 57]) with chronic total coronary occlusions (Thrombolysis in Myocardial Infarction trial 0) according to a protocol approved by the university's commission on ethical standards in medical research. All patients had given written consent. The patients had been selected according to the following angiographic and clinical criteria: (1) the duration of occlusion should be >1 month; (2) collateral filling of the vessel segments downstream of the occlu-

TABLE II Clinical Data of Patients with Successful and Unsuccessful Recanalization of Coronary Occlusions

	Successful	Unsuccessful
No. of patients	25	14*
Age (mean, range) (years)	58 (44–78)	55 (36–62)
Sex (male/female)	20/5	13/1
Prior myocardial infarction	16 (64%)	9 (64%)
Occluded vessel (right, LC, LAD)	14–6–5	6–3–5
Duration of occlusion (mo)	3.6 ± 3.2	5.5 ± 2.9†

* Twelve patients with failure of guidewire passage, 2 patients with failure of laser catheter passage.

† Significant difference between both groups according to the Mann-Whitney test ($p = 0.03$).

LAD = left anterior descending artery; LC = left circumflex artery.

sion from the opposite vessel during diagnostic angiography was required to determine the approximate course of the vessel; (3) a tortuous vessel or steep angles of vessel branchings were excluded because of the limited flexibility of the catheter; (4) at least 1 of 2 noninvasive tests (thallium or bicycle stress test, or both) should have indicated that the occlusion was responsible for exercise ischemia; and (5) the patient should not present with unstable angina.

The clinical data of patients with either successful or unsuccessful attempts of recanalization are summarized in Table II. The duration of the occlusion was determined from either the date of a prior myocardial infarction or a previous angiogram, or both.

All patients were receiving oral drug treatment of either a combination of nitrate and calcium antagonists, or nitrate and β blockers. Each patient received aspirin (100 mg/day) therapy, begun at least 1 week before the angioplasty. Before advancing the wire, a bolus of 10,000 IU heparin was given followed by intravenous heparin until removal of the sheath 24 hours later.

Data analysis: Numerical data are given as mean \pm standard deviation. Comparison of the clinical data of successful and unsuccessful recanalizations was done using the Mann-Whitney test. The residual stenosis after angioplasty was given as percent lumen diameter narrowing compared with the average of pre- and poststenotic segment diameters. The diameter was measured on a single plane representing the worst view of the lesion using an electronic caliper.

RESULTS

Primary success rate of coronary laser angioplasty: Percutaneous laser coronary angioplasty was attempted in 39 patients with chronic total coronary occlusions (Figure 1). In 7 patients (18%) it was not possible to pass the occlusion with a guidewire. In 3 patients (8%) the wire had caused a dissection at the site of the occlusion and therefore the procedure was stopped. In 2 patients (5%) the wire could not be advanced into the distal vessel segments after successful passage of a proximal occlusion, probably due to an additional stenosis distal to the occlusion. In 1 patient the recanalization wire was advanced into a septal branch of the left anterior descending artery. This led to the onset of ventricular tachycardia and then ventricular fibrillation that

had to be terminated by external defibrillation; the procedure was not continued after this event.

In 27 patients (69%) the laser catheter could be positioned proximal to the occlusion. In 25 patients (64%) the coronary laser angioplasty could be successfully performed as defined by the ability to pass the occlusion and create a new lumen of approximately the size of the catheter (Figure 2). In 2 patients the catheter did not pass the occlusion despite prolonged energy delivery and change of catheter size in 1 case. The subsequent attempt with a low-profile balloon catheter was also unsuccessful. The longer duration of the occlusion in pri-

mary unsuccessful recanalizations was the only difference compared with successful recanalizations ($p = 0.03$; Table II). The transmitted energy depended on the type of catheter as given in Table I. The energy output of the 4Fr catheter used in the first 6 patients decreased considerably after the procedure ($32 \pm 28\%$ loss of energy output). This had been improved by increased fiber quality in the following catheters (5Fr and 5.5Fr).

The average residual stenosis after laser was $61 \pm 17\%$ (Table III). In 6 patients with a residual stenosis of $<50\%$ no additional balloon angioplasty was done (Fig-

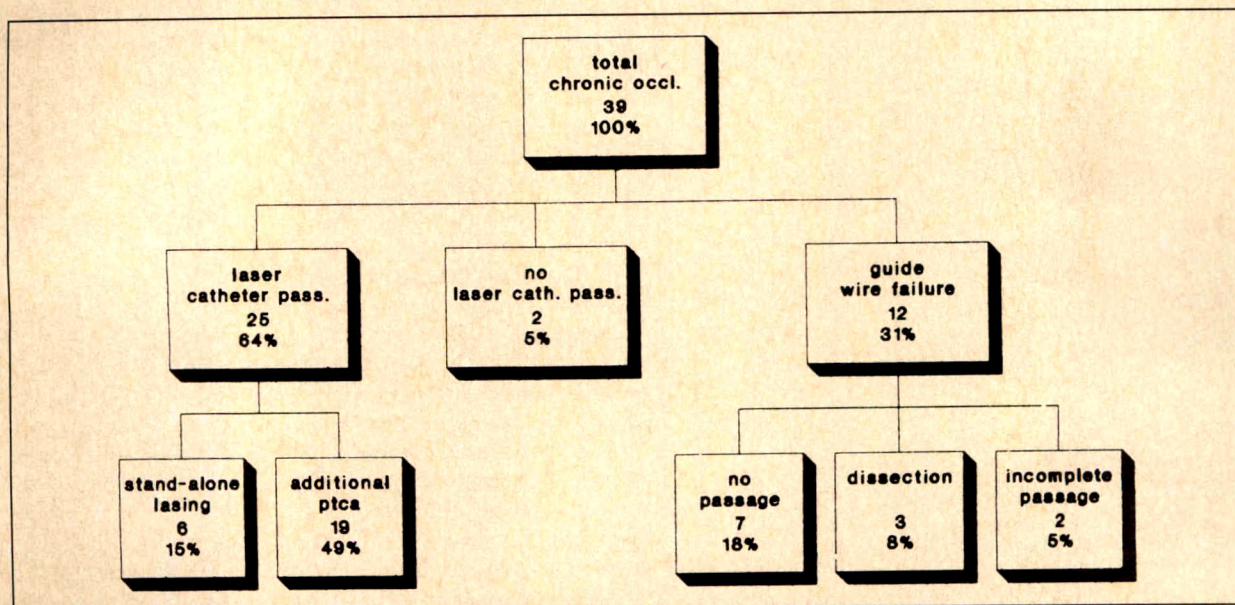


FIGURE 1. Overview of primary success of laser recanalization in 39 patients with total chronic coronary occlusions (occl.). cath. = catheterization; pass. = passage; PTCA = percutaneous transluminal coronary angioplasty.

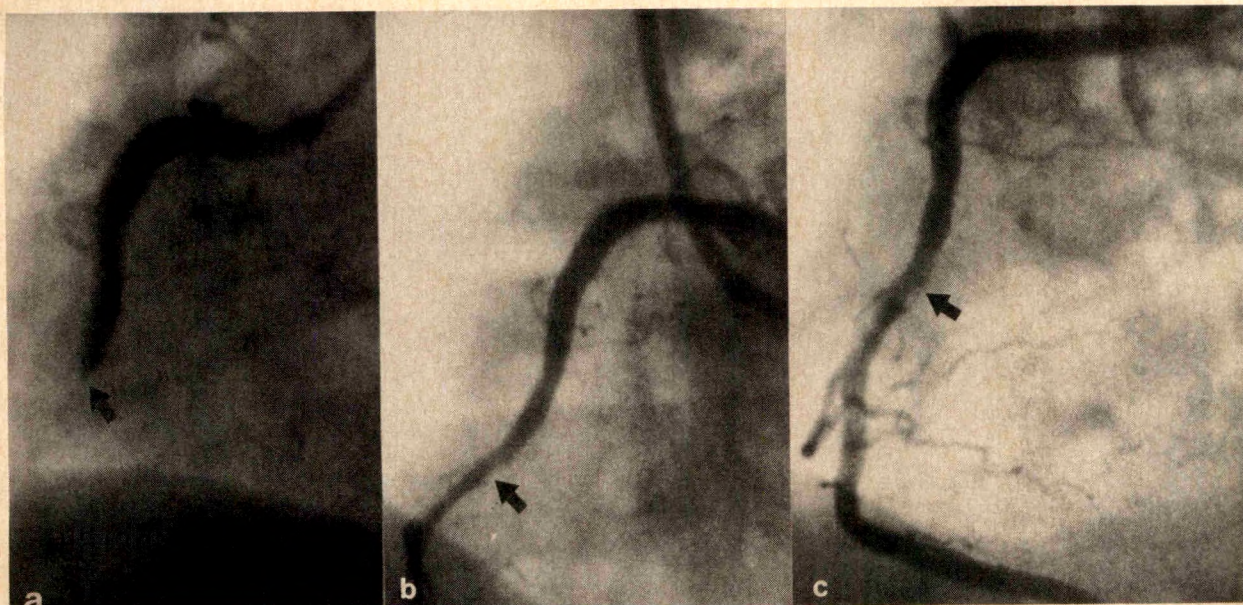


FIGURE 2. Laser-assisted recanalization of an occluded right coronary artery (a). After laser passage with a 4Fr catheter (b), the residual stenosis was considered to exceed 50% vessel diameter. After subsequent balloon angioplasty of 3.0 mm, there was no significant residual stenosis. After recanalization, a right ventricular branch is now perfused again.

TABLE III Summary of Successful Laser Recanalizations of Chronic Total Occlusions

Pt. No.	No. of Coronary Arteries Narrowed (>50%)	Coronary Arteries Occluded	Occlusion Duration (mos)	Occlusion Related Infarct	% Vessel Diameter After:	
					Laser	Balloon
1	1	Right	1	+	60	20
2	1	LC	6	+	75	30
3	2	LC	2	+	65	20
4	3	Right	3	+	60	45
5	3	Right	3	0	50	10
6	1	LAD	2	+	60	40
7	1	Right	4	+	65	20
8	3	Right	9	+	55	25
9	3	LAD	2	0	70	35
10	1	LC	1	+	45	—
11	3	LC	1	0	80	30
12	3	Right	12	+	75	20
13	3	Right	1	+	50	30
14	1	Right	3	+	40	—
15	1	LC	1	0	30	—
16	2	LC	4	0	90	25
17	1	LAD	2	+	65	40
18	2	Right	12	+	75	30
19	1	LAD	1	0	70	20
20	2	Right	3	+	80	35
21	2	LAD	2	0	35	—
22	3	Right	4	0	40	—
23	2	Right	1	+	80	30
24	2	Right	6	+	40	—
25	1	Right	3	0	70	20
3.6 ± 3.2					61 ± 17	28 ± 9

Values at the bottom represent mean ± standard deviation.
LAD = left anterior descending; LC = left circumflex; + = previous infarct; 0 = no previous infarct; — = no balloon angioplasty performed.

ure 3); in all other cases laser angioplasty was followed by conventional angioplasty resulting in a residual stenosis of $28 \pm 9\%$; the residual stenosis after stand-alone laser angioplasty was $38 \pm 5\%$. In 2 of 25 patients with primary successful laser recanalization (8%), the 24-hour control angiogram showed a reocclusion without clinical symptoms, indicating a still effective collateral flow. Both had been treated by laser and subsequent balloon angioplasty.

The functional result after recanalization was assessed by noninvasive stress tests, which had shown a pathologic result before the procedure. In 6 patients ST-segment depression was no longer visible in the respective electrocardiographic leads during bicycle stress test. In 14 patients the thallium stress test showed the disappearance of a previous ischemic zone during exercise. In 3 patients no change in the thallium stress test was observed, although their clinical symptoms had improved. The 2 patients with immediate reocclusion did not undergo a repeat stress test; in 1 of them bypass surgery was performed while the other continued to receive medical treatment.

Complications during coronary laser angioplasty:

None of the patients experienced a laser associated complication. The induction of a ventricular tachycardia and fibrillation in one case was caused by the guide-wire. During coronary laser angioplasty of a branch of the left coronary artery, 3 patients reported angina pectoris, which was due to the obstruction of smaller coronary branches when the laser catheter was advanced to the occluded segment. The patients did not experience any pain or discomfort during the delivery of laser energy. Occlusions of distal coronary vessel segments due to peripheral embolization were not observed, and none of

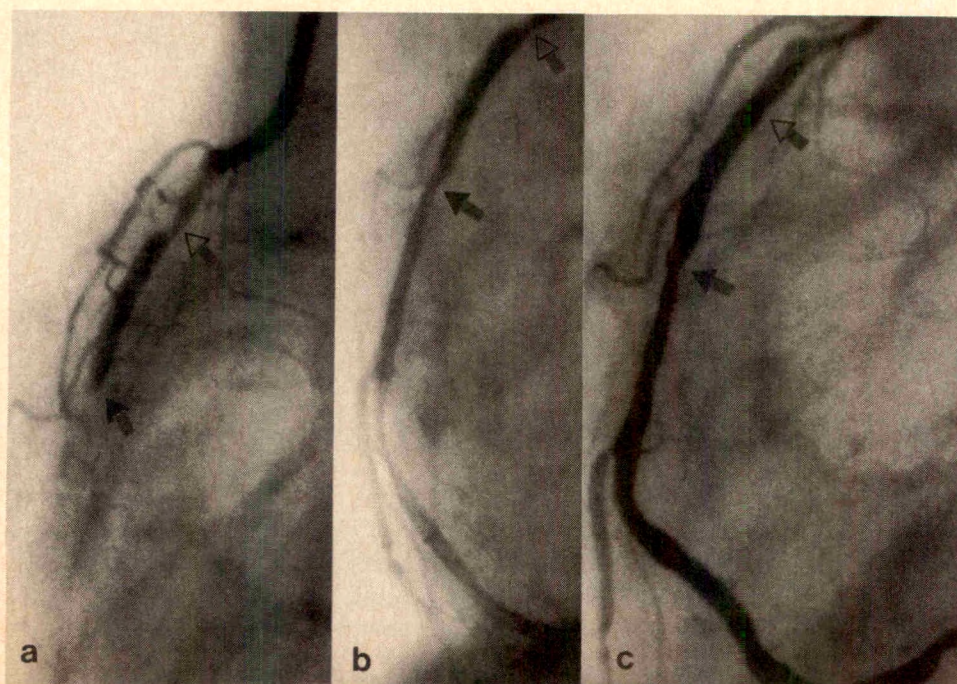


FIGURE 3. Laser angioplasty of an occluded right coronary artery (a). Both a proximal stenosis (open arrow) and an occlusion (full arrow) were recanalized successfully by a 5.5Fr catheter. The side branch just proximal to the stenosis identifies the vessel segments on the different frames. The narrow segment distal to the occlusion was not considered to represent spasm but rather reflected an early low forward flow (b); 24-hour control angiogram with satisfying results both at the site of the stenosis and the occlusion (c).

the patients had an increase in serum creatine kinase levels until 24 hours after the procedure. Local thrombosis or acute vessel occlusion during the procedure was not observed.

DISCUSSION

Most of the patients of this study had had myocardial infarction caused by the vessel occlusion. The presence of clinical symptoms and evidence of ischemia made them eligible for an angioplasty procedure. The primary success rate of conventional balloon angioplasty of chronically occluded vessels reported in previous studies ranged from 44 to 66%, the duration of the occlusion being a major determinant of the success.^{5,7} In our patients the primary success depended on the ability to pass the occlusion by a guidewire, which was achieved in 68%. A shorter duration of occlusion was present in successful recanalizations compared with unsuccessful procedures, which confirmed earlier observations with balloon recanalization.⁷ The danger of perforating the vessel wall by using the laser catheter without a guidance was considered too high¹⁷ and therefore was not tried when the wire could not be advanced.

Coronary laser angioplasty over a guidewire proved to be a safe technique without complications associated with the application of laser energy. Even though the degree of eccentricity of the occluding lesion could not be predicted from the diagnostic angiography, no perforation using the concentric catheter design was encountered. The reocclusion within 24 hours observed in 2 patients did not cause any clinical symptoms or electrocardiographic changes, indicating the still effective collateral circulation. These early reocclusions represent those that were observed among asymptomatic patients during follow-up by repeat angiography.⁵

Technical aspects and limitations of laser angioplasty of chronic total coronary occlusion: The theoretical advantage of laser angioplasty is the ablation of atherosclerotic and even calcified plaques without mechanical or thermal damage to the adjacent tissue.^{10,11,18,19} Since the introduction of percutaneous excimer-laser angioplasty into interventional cardiology, the development of both the technical specifications of the laser source and the catheter devices are still in motion. Among the limitations of this new technique is the principle of ablation on contact, which, however, together with the wire guidance ensures safety of the technique. Because the achieved lumen after laser recanalization depends on the diameter of the catheter, these factors account for the need of additional balloon dilatation in 76% of our patients.

During the early phase of the study a considerable loss of transmitted power was observed during the laser procedure due to wear-out of the fibers despite no visible damage or breaking. The threshold for the ablation of atherosclerotic tissue in vitro is 14 mJ/mm²,¹² and the threshold for calcified lesions is in the range of 50 mJ/mm² when energy is transmitted by a single bare fiber.¹⁹ The maximum energy fluency achieved by the applied laser catheter system as calculated per fiber sur-

face was in the same range, but as the concentric multiple fiber design of the catheter tip included dead space, the effective fluency was smaller. In vitro tests with the catheters had shown that the transmitted energy exceeded the ablation threshold by a factor of 2. Therefore, a loss of energy transmitted during the treatment might have led to the failure or only limited success of laser angioplasty. Additionally, a mechanical dotter effect was probably present in cases with considerable fiber wear-out. Considering the limited energy fluency currently available, highly calcified lesions are not likely to be ablated, and this may account for the primary failure of the laser procedure in 2 cases. Because there is destruction of the quartz fibers by higher laser energies, the increase of the pulse width is a suggested way to enhance the efficiency of the system.²⁰

The use of a guidewire lead to primary failures of recanalization in cases where it could not pass the stenosis. In these patients, laser angioplasty could be performed only if a guiding system were available to discriminate between normal and atherosclerotic tissue.^{21,22} The application of such a system in the coronary system with the specific problem of moving vessels in the beating heart is not in the foreseeable future.

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Prevalence and Prognostic Significance of Exercise-Induced Ventricular Arrhythmias After Coronary Artery Bypass Grafting

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Exercise-induced ventricular arrhythmias occur often after coronary artery bypass grafting (CABG), but their prognostic significance is unknown. Two hundred patients examined by exercise electrocardiography and cardiac catheterization (including left ventriculography, bypass graft and native coronary artery angiography) before and 3 months after CABG were prospectively followed up. Exercise-induced ventricular arrhythmias occurred more often after (49 of 200 patients, 24.5%) than before (32 of 200 patients, 16.0%) CABG ($p < 0.05$). There were no differences between the patients with and without ventricular arrhythmias in the prevalence of graft patency (79 vs 80%) or the postoperative ejection fraction (57 ± 9 vs $57 \pm 12\%$). Ten cardiac deaths occurred during the mean follow-up time of 61 ± 19 months, 8 of which were witnessed sudden cardiac deaths. All cardiac deaths occurred in patients who did not have exercise-induced ventricular arrhythmias after CABG. The postoperative ejection fraction was lower in the cardiac death patients ($42 \pm 16\%$) than in the survivors ($58 \pm 10\%$) ($p < 0.01$). No other clinical or angiographic variable predicted the occurrence of cardiac death. Thus, the prevalence of exercise-induced ventricular arrhythmias increases after CABG, but the occurrence of ventricular arrhythmias does not indicate an increased risk of cardiac death.

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Coronary artery bypass grafting (CABG) relieves angina and improves exercise capacity in most patients, but may not abolish ambient or exercise-induced ventricular arrhythmias.¹⁻⁴ The long-term prognostic significance of ventricular ectopic activity after CABG is largely unknown. We prospectively followed up 200 patients who had been examined by preoperative and postoperative exercise testing and in whom graft patency and left ventricular function had been assessed by cardiac catheterization 3 months after CABG. Our main purpose was to evaluate the effects of CABG on the prevalence of exercise-induced ventricular arrhythmias and to assess their long-term prognostic significance.

METHODS

The series consisted of 200 consecutive patients (177 men, 23 women, mean age 49 ± 7 years) who had undergone CABG and who performed exercise electrocardiography before and 3 months after surgery. The patients underwent recatheterization 3 months after CABG in order to evaluate the surgical results in terms of graft patency at that time. The patients gave their informed consent for these examinations. Clinical characteristics of the patients are summarized in Table I.

Catheterization examinations: All patients underwent left-sided cardiac catheterization and angiography before and 3 months after CABG. Selective coronary artery, vein graft angiograms and biplane left ventricular cineangiograms were recorded and interpreted as described earlier⁴ by the Judkins technique. The myocardial jeopardy index was used to quantify the myocardium at risk for ischemia after CABG. Anterior myocardial jeopardy was defined as significant stenosis ($>50\%$) of the left anterior descending coronary artery without a patent bypass graft supplying normal or hypokinetic anterior and/or septal left ventricular wall segments. Inferior jeopardy was present when a stenotic right coronary artery without a patent bypass graft supplied a normal or hypokinetic ("viable") inferior left ventricular segment, and posterior jeopardy was present when a stenotic circumflex coronary artery without a patent bypass graft supplied a normal or hypokinetic posterior wall segment. The range of the jeopardy index was 0 (no jeopardy) to 3 (all segments at jeopardy). The left ventricle was divided into 5 segments in the

right anterior oblique projection (anterobasal, anterolateral, apical, diaphragmatic and posterobasal), and into 2 segments in the left anterior oblique projection (posterolateral, septal). Each of the segments was coded for wall motion as being normal (1 point), hypokinetic (2 points), akinetic (3 points) or dyskinetic (4 points). The sum of the points for each segment was used as a scoring system for left ventricular contractility: 7 to 8 points, normal or mild contraction normality; 9 to 11, moderate contraction abnormality; ≥ 12 , severe contraction abnormality.

TABLE I Clinical, Angiographic and Perioperative Data on Patients With and Without Ventricular Arrhythmias After Coronary Artery Bypass Grafting

	With VA (n = 151)		Without VA (n = 49)	
	Before	After	Before	After
Age (years)	50 \pm 7		50 \pm 7	
Sex (f/m)	19/132		4/49	
Prior MI				
0	75 (50%)		21 (43%)	
1	57 (38%)		24 (49%)	
≥ 2	19 (12%)		4 (8%)	
NYHA class				
1-2	27 (18%)	127 (84%)	9 (18%)	42 (86%)
3-4	124 (82%)	24 (16%)	40 (82%)	7 (14%)
Medication				
Digitalis	54 (36%)	81 (54%)	21 (43%)	31 (63%)
Diuretic	46 (31%)	42 (28%)	13 (27%)	10 (20%)
Beta-blocking agent	133 (89%)	123 (81%)	44 (90%)	40 (82%)
Antiarrhythmic drug	8 (5%)	14 (9%)	11 (2%)	2 (4%)
Perioperative data				
Myocardial infarction		15 (10%)		1 (6%)
Pericarditis		30 (20%)		15 (32%)
Cardioplegia time (min)		86 \pm 25		84 \pm 22
Angiographic data				
1-VD	19 (13%)		4 (8%)	
2-VD	47 (31%)		13 (27%)	
3-VD	85 (56%)		32 (62%)	
Graft patency (%)		77 \pm 28		80 \pm 20
LVEDP (mm Hg)	14 \pm 6	15 \pm 6	14 \pm 6	13 \pm 5
LVEDVI (ml/m ²)	79 \pm 20	78 \pm 25	79 \pm 18	74 \pm 18
LVESVI (ml/m ²)	34 \pm 16	36 \pm 22	33 \pm 12	33 \pm 13
LVEF (%)	59 \pm 11	57 \pm 12	58 \pm 10	57 \pm 9
Jeopardy score				
0	5 (3%)	74 (49%)	2 (4%)	22 (45%)
1	36 (24%)	58 (38%)	14 (29%)	24 (49%)
2	65 (43%)	17 (11%)	25 (51%)	2 (4%)
3	46 (30%)	3 (2%)	8 (16%)	1 (2%)
Exercise data				
Duration (min)	6.1 \pm 3.1	8.2 \pm 3.3	6.7 \pm 2.8	8.4 \pm 3.7
Work load (W)	80 \pm 36	105 \pm 37	91 \pm 40	108 \pm 49
HRmax (beats/min)	109 \pm 22	125 \pm 23	111 \pm 23	132 \pm 28
SBPmax (mm Hg)	164 \pm 28	176 \pm 29	167 \pm 27	183 \pm 34
End point AP	95 (78%)	41 (29%)	28 (68%)	15 (40%)
ST segment \downarrow ≥ 1 mm	77 (51%)	31 (21%)	25 (51%)	15 (31%)

No significant differences in the values between the 2 groups.

AP = angina pectoris; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; NYHA = New York Heart Association; SBP = systolic blood pressure; VA = ventricular arrhythmias; VD = vessel disease.

Exercise tests: The patients performed the exercise tests on the day preceding each catheterization. The exercise protocol has been previously described.⁴ Ventricular arrhythmias were measured and analyzed manually and classified as simple or complex, as modified from Lown and Wolf.⁵ The duration of exercise, maximal work load in the bicycle exercise test and reasons for stopping the tests were noted.

Follow-up: A questionnaire was mailed to all patients. If a complete answer was not received, the patients, their relatives or primary physicians were contacted by telephone. In cases of death, a detailed analysis of the mode of death was performed by reviewing the patient records and autopsy data (if available) and by questioning witnesses about the events preceding the death. Deaths were classified as cardiac and noncardiac, the cardiac deaths being regarded as sudden if they occurred within 1 hour of the onset of symptoms.

Statistics: The standard *t* test or Mann-Whitney test, when appropriate, was used to compare the continuous data between the groups. The chi-square test or Fisher's exact test was used to compare the proportions. The paired *t* test was used to compare preoperative and postoperative continuous data.

RESULTS

Prevalence of exercise-induced ventricular arrhythmias before and after bypass surgery: Exercise-induced ventricular arrhythmias occurred more often after CABG (49 of 200 patients [24.5%] after CABG vs 32 of 200 [16%] before CABG, *p* < 0.05) (Figure 1). The proportion of ventricular arrhythmias that were complex tended to be greater before than after CABG (10 of 32 [32%] vs 10 of 49 [20%], *p* = 0.07). New ventricular arrhythmias occurred in 37 of 200 patients (18.5%) after CABG.

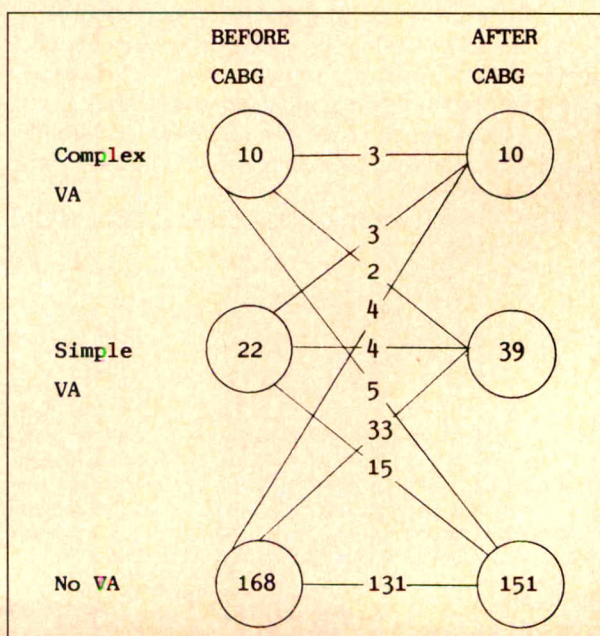


FIGURE 1. Frequencies of exercise-induced simple and complex ventricular arrhythmias (VA) before and after coronary artery bypass grafting (CABG).

Relation of postoperative ventricular arrhythmias to clinical and angiographic features: Table I compares the clinical and angiographic data for the patients with exercise-induced ventricular arrhythmias after CABG (group 1, $n = 49$) and without ventricular arrhythmias (group 2, $n = 151$). None of the clinical features differed between the 2 groups before or after CABG, nor was any difference seen in the angiographic severity of coronary artery disease or the preoperative and postoperative ejection fractions. Graft patency and the myocardial jeopardy index similarly did not differ between patients with or without ventricular arrhythmias after CABG. No differences in maximal work load or the prevalence of ST-segment depressions were detected between the groups during the exercise testing.

Follow-up data: There were 10 cardiac deaths during the mean follow-up period of 60 months (incidence 5.0%). Eight of the deaths (80%) were witnessed as being sudden cardiac deaths, and 2 patients died of myocardial infarction (20%). Table II compares the data for the survivors and those who died during the follow-up period. All the cardiac deaths occurred in patients who did not have exercise-induced ventricular arrhythmias after CABG.

Diuretic treatment was given more often to the patients who died; they received β -blocking therapy less frequently. Enlarged cardiac size, as assessed by x-ray, was seen more often in the cardiac death patients than in the survivors. No other clinical features differed between the groups. The postoperative left ventricular ejection fraction was lower in the patients who died; left ventricular volumes and end-diastolic pressures were higher and graft patency tended to be lower (Table II).

DISCUSSION

Exercise-induced ventricular arrhythmias occurred more often after CABG in this series, although it was apparent that the prevalence of complex ventricular arrhythmias tended to decrease after CABG. This finding is in agreement with previous reports, which have proposed that frequent exercise-induced ectopy after CABG may be related to prior myocardial infarction and improved exercise capacity.^{1,4} However, no such associations were evident in this group. No data have been available on the relation between the occurrence of ventricular arrhythmias and angiographic results after CABG. No differences in the prevalence of graft patency or left ventricular function after CABG were seen between the patients with and without ventricular arrhythmias, and thus the occurrence of ventricular arrhythmias after CABG does not appear to be related to occlusions of the bypass grafts or deterioration in ventricular function. Exercise tolerance was better and maximal heart rate and blood pressure were higher after CABG. It is possible that higher work load and increased sympathetic activity during exercise may account for the increased ectopic activity after CABG.

The most important result was that exercise-induced ventricular arrhythmias after CABG do not have any long-term prognostic significance for cardiac mortality. In fact, none of the patients who had ventricular arrhythmias after CABG died during the follow-up.

These findings concur with those of earlier reports on smaller patient populations and with shorter follow-up times,^{1,6} namely, that exercise-related ventricular arrhythmias are not associated with an increased risk of cardiac mortality after CABG.

The reproducibility of exercise-induced ventricular arrhythmias is not very high,⁶⁻⁸ a fact that probably influenced our results. However, recent evaluations using ambulatory recordings also have shown that ventricular

TABLE II Comparison of Postoperative Data Between Survivors and Cardiac Death Cases

	Survivors ($n = 190$)	Cardiac Death Cases ($n = 10$)	p Value
Clinical data			
Age (years)	50 ± 7	53 ± 8	NS
NYHA class			
I-II	160 (85%)	8 (80%)	NS
III-IV	30 (15%)	2 (20%)	NS
Medication			
Digitalis	104 (55%)	8 (80%)	NS
Diuretic	45 (24%)	7 (70%)	$p < 0.01$
Beta-blocking agent	158 (83%)	5 (50%)	$p < 0.05$
Calcium antagonist	34 (18%)	2 (20%)	NS
Antiarrhythmic drug	14 (7%)	2 (20%)	NS
Prior MI			
0	92 (48%)	4 (40%)	NS
1	76 (40%)	5 (50%)	NS
≥ 2	22 (12%)	1 (10%)	NS
Cholesterol (mmol/liter)	7.3 ± 1.5	6.5 ± 1.7	NS
HDL cholesterol (mmol/liter)	1.0 ± 0.8	1.0 ± 0.3	NS
Triglycerides (mmol/liter)	2.3 ± 1.6	1.8 ± 1.3	NS
Electrocardiogram			
Q waves	71 (38%)	7 (70%)	NS
Bundle branch block	28 (15%)	3 (30%)	NS
Left ventricular hypertrophy	2 (1%)	0	NS
Chest x-ray			
Enlarged cardiac size	84 (44%)	9 (90%)	$p < 0.01$
Congestion	5 (3%)	1 (10%)	NS
Angiographic data			
Graft patency (%)	79 ± 26	62 ± 34	$p < 0.05$
No. of grafts/patient	3.1 ± 1	3.3 ± 1.1	NS
Jeopardy score			
0	91 (48%)	4 (40%)	NS
1	78 (41%)	3 (30%)	NS
2	17 (9%)	2 (20%)	NS
3	4 (2%)	1 (10%)	NS
Contractility score			
7-9	148 (78%)	4 (40%)	$p < 0.05$
9-11	21 (11%)	4 (40%)	NS
≥ 12	21 (11%)	2 (20%)	NS
Left ventriculogram			
LVEDP (mm Hg)	14 ± 6	20 ± 5	$p < 0.01$
LVEDVI (ml/m ²)	75 ± 20	109 ± 45	$p < 0.001$
LVESVI (ml/m ²)	33 ± 16	70 ± 44	$p < 0.001$
LVEF (%)	58 ± 10	42 ± 16	$p < 0.01$
Exercise data			
Duration (min)	8.3 ± 3.5	7 ± 2.3	NS
Work load (W)	106 ± 40	100 ± 32	NS
HRrest (beats/min)	74 ± 13	66 ± 8	NS
HRmax (beats/min)	127 ± 24	128 ± 20	NS
SBPrest (mm Hg)	136 ± 18	137 ± 17	NS
SBPmax (mm Hg)	178 ± 31	173 ± 23	NS
End point AP	54 (32%)	2 (20%)	NS
ST segment $\downarrow \geq 1$ mm	45 (24%)	4 (40%)	NS
Ventricular ectopy	49 (26%)	0	NS

HDL = high-density lipoprotein; MI = myocardial infarction; NS = not significant; other abbreviations as in Table I.

ectopy occurs more often after CABG, but this does not indicate an increased risk of death.^{9,10} Thus, there appears to be no indication for suppressing the ventricular ectopy after CABG for prognostic reasons.

The fact that none of the exercise data, not even the ST-segment changes or improvements in exercise capacity, differed between the survivors and the patients who died suggests that postoperative exercise testing is of limited value for predicting cardiac mortality after CABG. Dubach et al¹¹ also found that exercise testing may not be useful for identifying patients with future cardiac events after CABG.

The cardiac death patients tended to have symptoms of cardiac failure after CABG more often than the survivors, and their left ventricular function was more impaired. Thus, depressed left ventricular function still appears to be the major risk factor for cardiac death even after CABG.

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Temporal Relation Between Left Ventricular Dysfunction and Chest Pain in Coronary Artery Disease During Activities of Daily Living

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Forty-three ambulatory patients with angina of increasing frequency underwent continuous monitoring of left ventricular (LV) function for an average of 2.9 ± 1.9 hours to determine the incidence and temporal sequence of LV dysfunction, ST-segment depression and chest pain. Indicators of ischemia were: a decrease in ejection fraction $>5\%$ lasting >1 minute; horizontal or downsloping ST-segment depression of ≥ 1 mm; or onset of the patient's typical chest pain complex, or a combination of these. During the monitoring interval, subjects performed daily activities such as sitting, walking, climbing stairs and eating. In 11 patients, 22 episodes of chest pain or ST-segment depression, or both, were observed. Eighteen episodes were accompanied by a decrease in ejection fraction (9 patients); chest pain accompanied the decrease in ejection fraction during 13 episodes, whereas ST-segment changes occurred during 7. In 12 of 13 episodes the decrease in ejection fraction began earlier than the onset of chest pain, whereas in 1 patient ejection fraction decrease and chest pain onset started at the same time. The average interval from a decrease in ejection fraction to the onset of chest pain was 56 ± 41 seconds (range 0 to 120). ST changes occurred after the onset of a decrease in ejection fraction in 6 of 7 episodes. The average interval from the onset of ejection fraction decrease and the onset of ST change was 99 ± 91 seconds. These data suggest that LV dysfunction manifested by a decrease in ejection fraction is an earlier indicator of myocardial ischemia than is angina pectoris or electrocardiographic evidence of ischemia.

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Chest pain is one of the most common symptoms that cause patients to seek medical attention for suspected coronary artery disease. Recent studies suggest, however, that this symptom does not occur in most episodes of myocardial ischemia. When diagnostic ischemic changes on electrocardiography were used as a criteria, only 25% of the episodes of ST-segment changes were accompanied by chest pain^{1,2}; studies using an ambulatory ventricular function monitor suggested that 64% of episodes of a transient decrease in left ventricular (LV) ejection fraction were not accompanied by chest pain; finally, in patients monitored in an intensive care unit with simultaneous measurement of electrocardiographic changes and LV pressures, ischemia was present for an average of 3 minutes before chest pain occurred.³

Myocardial ischemia without symptoms presents a major conundrum for the management of patients with coronary artery disease. Ischemia is usually associated with impaired LV function, leading to the supposition that ischemic episodes should be treated even if they are not symptomatic. Therapy of ischemic coronary artery disease is usually directed toward the elimination of symptoms, thereby suggesting that silent episodes are less important and need not be treated. There is some merit to both of these arguments: Severe ischemia should depress ventricular function, regardless of electrocardiographic changes or associated chest pain, whereas mild episodes of ischemia should produce minimal impairment of LV function independent of the severity of electrocardiographic changes or chest pain. Before considering the possible efficacy of therapy in silent ischemia, the incidence and temporal relation of its hallmarks, LV dysfunction, ST depression and chest pain, should be documented. This study applied a new ambulatory ventricular function monitor to 43 patients with documented severe coronary artery disease to determine this sequence of events.

METHODS

Patients: Forty-three patients (38 men and 5 women, mean age 60 years, range 45 to 78) with chest pain requiring hospitalization, who had coronary artery disease defined as a diameter reduction of $>50\%$ documented by coronary angiography, were studied with an ambulatory ventricular function monitor before hospital discharge. Ten patients had 1-, 8 had 2- and 25 had 3-vessel disease. Thirty patients had a history of myocar-

dial infarction and 11 had undergone coronary artery bypass graft surgery. All patients continued their usual medication during the recording interval.

Ambulatory monitoring: After intravenous injection of stannous pyrophosphate, the patient's red blood cells were labeled with 20 to 30 mCi of technetium-99m using a modified *in vivo* method.⁴ Gated blood pool scans were recorded in the anterior and left anterior oblique projections as part of the evaluation of each patient's known heart disease. At the conclusion of blood pool scintigraphy, the detector of the ambulatory ventricular function monitor was positioned over the LV blood pool as previously described.⁵ Briefly, a firm plastic, vest-like garment was placed over the thorax. While the patient sat in front of the detector of the scintillation camera in the left anterior oblique position, the detector was carefully positioned to eclipse the LV blood pool and was locked in its holder in the garment. Electrodes for ambulatory electrocardiography were attached to record a modified V₅ lead in parallel with the LV time-activity curve in the ambulatory monitor. The recorder was started and the patient instructed in the use of the event marker. The beat-to-beat LV time activity curve, sampled at 31-ms intervals, and the electrocardiogram were recorded on tape. Events marked on the tape included: (1) the start or stop of activities—e.g., walking, sitting, climbing stairs, and so forth; (2) the onset of chest pain; (3) the time of peak severity; and (4) the time of cessation of pain. At the end of ambulatory function data recording, static images were again recorded with the scintillation camera to verify detector positioning. The ambulatory ventricular function tape was read into a minicomputer (PDP 11/73; Digital Equipment Corp) for analysis.⁵

Data analysis consisted of evaluating the radionuclide data as previously described⁵ and plotting the calculated ejection fraction, ST-segment analysis and event marks versus time. A significant decrease in LV ejection fraction was defined as a decrease of >5 ejection fraction units lasting >1 minute. A horizontal or downsloping ST segment of >0.1 mV lasting >30 seconds on the electrocardiogram was considered significant. The interval from the onset of a significant decrease in ejection fraction or ST segment to the onset of a chest pain event marker was determined.

RESULTS

The average recording time was 2.9 hours (range 0.3 to 12). A representative trend analysis of 1 patient during angina is shown in Figure 1. The initial ejection fraction and heart rate were 62% and 81 beats/min, respectively. After walking up stairs, the heart rate increased to 99 beats/min but the ejection fraction decreased to 47%, followed by the onset of chest pain. After resolution of chest pain, the ejection fraction returned to the preischemic value.

Twenty-two episodes of angina pectoris, or ST-segment depression, or both, were observed in 11 patients: 3 episodes of chest pain were not associated with a transient decrease in LV ejection fraction or ST depression; 1 episode of ST depression was not accompanied by either a decrease in LV ejection fraction or chest pain; 18 episodes (in 9 patients) of a decrease in LV ejection fraction of $\geq 5\%$ lasting ≥ 60 seconds were associated with angina pectoris, or ST-segment depression, or both. The temporal relation of the onset of ejection fraction decrease to the onset of angina, ischemic ST change and maximal ejection fraction decrease in these 9 patients

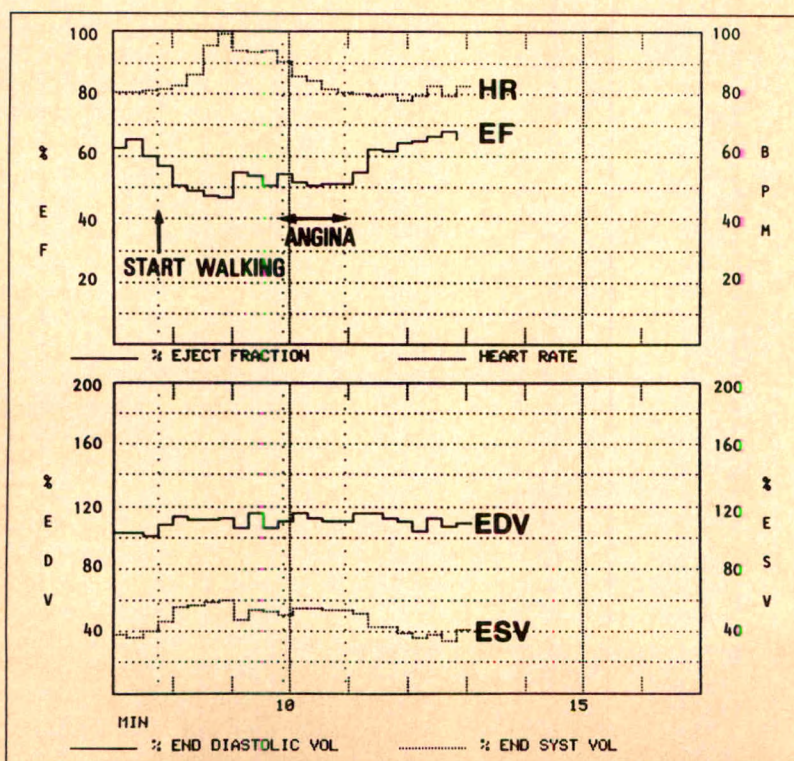


FIGURE 1. Trendgram depicting minute 7 to minute 13 of a recording from patient no. 2. Average ejection fraction (EF) (solid line), heart rate (HR) (dashed line) are shown in the upper panel, while the relative end-diastolic volume (EDV) (solid line) and relative end-systolic volume (ESV) (dashed line) are shown in the bottom panel. The patient began walking upstairs at 7.7 minutes, associated with an increase in heart rate of 18 beats/min (BPM). Average ejection fraction (solid line) began to decrease at the onset of ambulation, whereas chest pain occurred 110 seconds later. ST-segment depression (not shown) began 15 seconds after the onset of ejection fraction decrease. Resolution of chest pain preceded the return of ejection fraction to the baseline value.

TABLE I Time Delay to the Onset of Angina, ST Change and Maximal Ejection Fraction Decrease from the Onset of Ejection Fraction Decrease

Pt. No.	Ep.	ST Angina (s)	Time Delay to		Duration EF Decrease (s)	Maximum EF Decrease (%)	Activity
			EF Change (s)	Maximum EF Decrease (s)			
1	a	120	105	165	315	20	Walking
	b	—	75	0	75	6	Sitting
2	a	110	15	45	195	15	Stair
	b	—	75	90	150	15	Walking
3	a	45	—	45	120	12	Bicycle
	b	15	—	15	75	6	Walking
	c	15	—	15	90	6	Bicycle
4	a	60	*	135	240	11	Stair
	b	105	*	120	270	12	Walking
	c	105	*	90	300	10	Walking
5		0	—	0	60	6	Sitting
6	a	30	—	90	180	15	Walking
	b	60	—	120	420	15	Sitting
7		30	—	30	105	8	Walking
8		30	—	0	90	6	Walking
9	a	—	270	210	300	8	Walking
	b	—	150	120	180	8	Walking
	c	—	0	0	90	6	Walking
Mean \pm SD		56 \pm 41	99 \pm 91	72 \pm 64	181 \pm 105	10.3 \pm 4.3	

* ST change could not be evaluated because of the presence of left bundle branch block.
EF = ejection fraction; Ep. = episode; SD = standard deviation.

are summarized in Table I. In 2 patients with 1 episode of chest pain each, the onset of angina, ST-segment depression and decrease in LV ejection fraction occurred concurrently. In 6 patients, 11 episodes of LV dysfunction were manifest by a transient decrease in LV ejection fraction associated with their characteristic chest pain, but without ST-segment changes. ST-segment depression could not be evaluated during 3 episodes of ejection fraction decrease with angina, because of left bundle branch block (patient 4). In 5 episodes in 3 patients, a decrease in ejection fraction was associated with ST-segment depression, but without chest pain. The average decrease in ejection fraction was 10 points (range 6 to 20) and had a duration of 181 ± 105 seconds. The decrease in ejection fraction was gradual, requiring 72 ± 64 seconds from the time of onset to the nadir of ejection fraction for that episode. In 12 of the 13 episodes of chest pain and decreased ejection fraction, the onset of angina pectoris was preceded by a decrease in LV ejection fraction. In 1 episode the LV ejection fraction decrease began simultaneously with the onset of angina pectoris. The average time difference from a decrease in ejection fraction to the onset of angina pectoris was 56 ± 41 seconds (range 0 to 120). In 5 episodes, angina occurred at the time of nadir of the ejection fraction decrease; in 5 episodes it occurred before the nadir of the ejection fraction decrease, whereas in 3 episodes it occurred during recovery of ejection fraction. The average time interval from the onset of ejection fraction decrease to its nadir in the episodes with angina was 67 ± 56 seconds.

In 6 of 7 episodes of transient ejection fraction decrease with ST change, ST-segment depression oc-

curred after the onset of ejection fraction decrease. The average time difference between the onset of ejection fraction decrease and ST change was 99 ± 91 seconds. In 2 patients, 2 episodes of a transient decrease of ejection fraction with chest pain and ST segment change were noted, where the ejection fraction decrease began first, followed by ST-segment depression, followed by chest pain. The return to normal LV ejection fraction followed a similar time course, where relief of chest pain preceded the normalization of LV ejection fraction.

DISCUSSION

The aim of this study was to determine the temporal relation between LV dysfunction, manifested by a decrease in LV ejection fraction, angina pectoris, and ST-segment changes as evidence of myocardial ischemia in a group of subjects with documented severe coronary artery disease.

Recent invasive animal studies showed that LV dysfunction due to myocardial ischemia occurred before the appearance of electrocardiographic ST-segment changes,⁶⁻⁹ or, in moderate stenosis, without ST-segment changes.¹⁰ During percutaneous transluminal coronary angioplasty in 18 patients, Hauser et al¹¹ showed that dyskinesia detected by echocardiography began 19 ± 8 seconds after coronary artery occlusion in 86% of procedures, whereas ST-segment changes occurred 30 ± 5 seconds after occlusion in 36% of the procedures. ST changes invariably occurred after wall motion abnormalities, and preceded or accompanied the onset of chest pain. Using echocardiography, Sugishita et al¹² reported decreases of LV posterior wall or interventricular septum excursion earlier than ST-T changes in 15

patients but simultaneously in 2 during supine bicycle ergometer exercise. During ergonovine testing in patients with Prinzmetal angina, Distant et al¹³ used echocardiography to identify wall motion abnormalities before the onset of ST changes, followed by anginal pain.

Similar results have been obtained in clinical studies using radionuclide methods. O'Hara et al¹⁴ demonstrated a decrease in ejection fraction with the nuclear stethoscope that was detectable before the appearance of ST segment depression in 11 of 12 patients with stable angina pectoris during semisupine bicycle exercise. Upton et al¹⁵ showed a decrease, or increase of <5% points of ejection fraction, in 18 of 25 patients before the electrocardiographic evidence of ischemia using repeated radionuclide first-pass angiography at rest and during 2-step upright bicycle exercise. They also demonstrated abnormalities of LV function before the onset of angina pectoris, with no patient having angina pectoris before the onset of ST-segment depression.

These angioplasty, echocardiographic and radionuclide studies are in keeping with our results in ambulatory patients: LV dysfunction started earlier than angina or ST changes in the majority of subjects. LV dysfunction is likely to be a more sensitive indicator of ischemia, because 8 episodes of ejection fraction decrease occurred without significant ST changes. These episodes were suggestive of ischemia for 2 reasons: first, previous data in healthy volunteers did not find a decrease in ejection fraction during the same activities performed by the patients in this trial⁵; and second, the episodes were usually accompanied by the patients' typical anginal pain. It may be argued that this early version of the ventricular functional monitor did not monitor 2 leads of the electrocardiogram and that the sensitivity of our electrocardiographic data is therefore artifactually low. However, a more likely explanation is that some episodes of ischemia are not accompanied by electrocardiographic changes. Sayen et al¹⁶ showed that, with occlusion of the small coronary branches in dogs, epicardial electrocardiographic changes may be insignificant, even in the presence of contractile disturbances, and Battler et al¹⁰ observed regional ventricular dysfunction without surface electrocardiographic changes in experimental studies of coronary stenosis in dogs. In this study, 3 episodes of angina were associated with neither a decrease in ejection fraction nor ST-segment depression. Whether these episodes involved very small areas of myocardium, and thus were not associated with either a decrease in global function or changes in the surface electrocardiogram, or had some other etiology, is uncertain.

The temporal relation between the appearance of ST change as evidence of ischemia and occurrence of angina pectoris is still controversial. In addition to Hauser,¹¹ Distant¹³ and their co-workers, Linhart,¹⁶ Levy¹⁷ and their co-workers showed ST-segment changes occurring earlier than angina pectoris. However, Cecchi,¹⁸ Amsterdam¹⁹ and their associates observed that ST-segment changes did not always precede angina during ex-

ercise. In our study, only 2 patients had ST changes and angina pectoris; in both patients the ST change preceded angina pectoris.

The ventricular function monitor couples radionuclide techniques with Holter monitoring to provide a continuous beat-by-beat recording of cardiac function and electrocardiographic changes during the performance of daily activities. Previous studies with this instrument and its predecessors demonstrated a good correlation between the measurement of LV ejection fraction using the ventricular function monitor system and that recorded with multigated imaging.²⁰

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Recanalization of Chronic, Totally Occluded Coronary Arteries by New Angioplasty Systems

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The benefit and safety of new angioplasty equipment as compared with the conventional guidewire approach was evaluated in 154 consecutive patients with chronic, totally occluded coronary arteries. The protocol followed a stepwise design: first, conventional guidewires and low-profile balloons were used, followed by "balloon-on-the-wire" systems (Probe™, Ace™) or by a shaft-enforced, tip-deflecting catheter (Omniflex™). In 97 patients with occlusions of 2 to 12 weeks' duration, recanalization was achieved in 51 patients (53%) with the conventional approach and in 29 patients with the new devices (balloon-on-the-wire [n = 5], Omniflex [n = 24]), thereby raising the success rate to 82%. In 57 occlusions of >12 weeks' duration, the recanalization attempt was successful in 58%, mediated in 16 patients (28%) by the Omniflex catheter and in 5 patients by balloon-on-the-wire systems. There were no life-threatening complications and only 1 (0.6%) emergency bypass operation was necessary. New angioplasty devices are therefore of considerable value in the attempt to improve the results of coronary angioplasty in chronic total occlusions.

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Coronary angioplasty of high-grade stenoses is performed today in experienced centers at a success rate of >90%.^{1,2} The same primary success rate is achieved in fresh thrombotic occlusions, such as those seen in acute myocardial infarctions.³⁻⁵ In contrast, success rates in chronic total occlusions are in the range of only 60%.⁶⁻¹⁴ These results are not markedly improved when conventional guidewires are enforced and stabilized by balloon or reperfusion catheters.¹⁵ Recently, however, new angioplasty systems, with potentially useful designs for the recanalization of chronic total occlusions, have been introduced. High stability, exact torque control and a low profile appear to be the features essential for finding the correct channel and for pushing the system through the occluded segment for inflation of the balloon.^{16,17} In the current study, the benefit and risk of new devices were evaluated in patients in whom the conventional technique failed.

METHODS

Patient population: Between January 1987 and January 1990, 154 consecutive patients (32 women, 122 men; aged 56 ± 10 [mean ± 1 standard deviation] years) were admitted to the University Hospital Hamburg for elective recanalization of total coronary artery occlusions by angioplasty. To be included in the study, the following entry criteria had to be fulfilled: estimated duration of occlusion of ≥ 2 weeks; stable angina pectoris or electrocardiographic or scintigraphic evidence of ischemia related to the target vessel; and complete occlusion (Thrombolysis in Myocardial Infarction flow grade 0) of a major coronary artery without a visible intraluminal channel, but with some retrograde or anterograde opacification of the distal segment via collateral vessels. Patients with subtotally occluded vessels, regarded as functional occlusions by others,^{9,13} were not included.

Study protocol: Recanalizations were performed with surgical back-up. In all patients, the femoral approach was used with large lumen 8Fr catheters (Interventional Medical). Special care was taken to choose a guiding catheter that provided good back-up with a stable ostial position. All patients were pretreated with aspirin and received 5,000 IU of intracoronary heparin bolus at the beginning of the procedure, and another 10,000 IU when the occlusion was crossed.

According to the protocol (Figure 1), 0.012-, 0.014- and 0.018-inch conventional guidewires, first of floppy texture and then of standard stiffness (Schneider, Advanced Cardiovascular Systems) were advanced to the

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TABLE I Success Rates by Vessels

Coronary Artery	2-12 Weeks	>12 Weeks
Left anterior descending	33/42 (79%)	14/19 (74%)
Conventional	24	8
"Balloon-on-the-wire"	3	3
Omniflex™	6	3
Left circumflex	14/17 (82%)	6/8 (75%)
Conventional	8	2
"Balloon-on-the-wire"	2	1
Omniflex™	4	3
Right	32/37 (86%)	13/30 (43%)
Conventional	18	2
"Balloon-on-the-wire"	0	1
Omniflex™	14	10

occlusion. When, within a limit of 10-minute fluoroscopy, the entrance port was found and passage achieved with a guidewire, a balloon of adequate size was placed in the lesion to open the vessel. If it was not possible to push a 2.0-mm USCI Mini-Profile™ balloon across the occluded segment, the wire was exchanged for a USCI Probing™ catheter followed by a USCI Probe™ (1-cm tip) balloon.¹⁸ In 2 patients, an Ace™ (Sci Med) balloon-on-the-wire system was introduced as the alternative (after July 1989).

When the occlusion was not crossed by any wire, a 2- or 2.5-mm Omniflex™ system (Medtronic) was introduced (Figure 1). This fixed wire device is enforced by a spring coil and thereby provides superior pushability. In addition, the tip can be deflected by an external handle and is thereby pointed toward the target lumen. In 3 patients in whom the Omniflex™ failed to cross the lesion, the Magnum Meier™ system (Schneider) was used (after September 1989). This system was developed es-

pecially for chronic total occlusions.¹⁶ The procedure was abandoned when, after a total of approximately 15 minutes of fluoroscopy, no success was achieved or a major complication (long dissection) was encountered.

Definitions: Duration of the occlusion was estimated by the date of myocardial infarction or by marked, abrupt change in the pattern of angina. In 10 patients, the duration could not reliably be determined but, according to the previous diagnostic catheterization, lasted >2 weeks although most likely not >3 months.

A recanalization was regarded as successful when full antegrade flow (Thrombolysis in Myocardial Infarction flow grade 3) with a residual stenosis <50% in diameter in ≥ 2 views by caliper measurements could be established as the final result.

A dissection, defined according to the National Heart, Lung, and Blood Institute registry criteria,¹⁹ was considered as a complication.

Follow-up: All patients routinely received aspirin (100 mg/day) after hospital discharge. Because of known adverse reactions to aspirin, 2 patients received warfarin. In 52 consecutive patients who underwent successful recanalization after July 1, 1988, repeat angiograms were routinely obtained 3 months after successful recanalization or after recurrence of symptoms. The interval of 3 months was used because of an expected higher success rate for potential repeat recanalizations.

Statistical analysis: Data are expressed as mean \pm 1 standard deviation. Differences in outcome of recanalization were tested by means of the chi-square test.

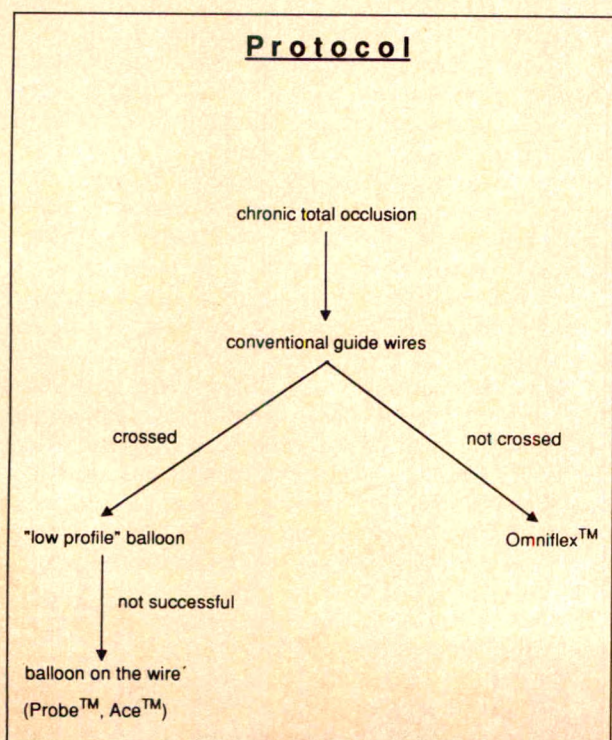
RESULTS

Patient characteristics: Of the 154 consecutive patients, 84 had a history of transmural myocardial infarctions related to the occluded vessel. The coronary arteries attempted were: left anterior descending, including large diagonal branches (n = 61; 40%); left circumflex, including large marginal branches (n = 25; 16%); and right coronary arteries (n = 67; 43%). In 1 patient, a saphenous vein graft was the target vessel.

The patients were subdivided, based on American College of Cardiology/American Heart Association guidelines,¹ into groups A and B, according to the estimated duration of occlusion (Table I). Group A comprised 97 patients (22 women, 75 men; mean age 55 ± 10 years) with vessels occluded from 2 to 12 (mean 6 ± 3) weeks. In group B, the 57 patients (10 women, 47 men; aged 57 ± 9 years) had occlusions older than 12 weeks (mean 22 ± 9 , range 13 to 52).

Acute angiographic results: Successful recanalizations with a residual stenosis <50% in diameter were achieved in 113 (73%) of 154 of all attempted occlusions.

In group A, 51 (53%) of 97 vessels could successfully be recanalized with conventional guidewire systems and low-profile balloons. In 5 patients, the occluded segment could only be crossed by a wire, but not by a 2-mm low-profile balloon. All these occlusions were successfully opened by balloon-on-the-wire systems (n = 4 with Probe, n = 1 with Ace). Of the 41 occlusions in group A not crossed with guidewires, 24 could be recanalized

**FIGURE 1.** Study protocol.

with the Omniflex system, thereby increasing the total success rate in this group to 82% (Figure 2).

In group B, only 12 (21%) of 57 occlusions were successfully recanalized with conventional angioplasty equipment. A balloon-on-the-wire system was success-

fully applied, according to the protocol, in 5 occlusions ($n = 4$ with Probe, $n = 1$ with Ace). Of the 40 lesions not crossed with these systems, 16 (28%) could still be recanalized with the Omniflex system. None of the 3 vessels unsuccessfully attempted with Omniflex could be recanalized with the Magnum Meier system. The final success rate therefore reached 58% in this group and was thereby significantly lower ($p < 0.001$) than in group A. The oldest occlusion that could be opened had persisted for 32 weeks (Figure 3).

Complications: There was no major complication, such as death, vessel perforation or Q-wave infarction. One patient (0.6%) required immediate bypass surgery due to acute thrombotic occlusion of a large diagonal branch during recanalization of the left anterior descending artery. In 7 (4%) patients ($n = 1$, 0.014-inch guidewire; $n = 6$ [7%, Omniflex]), a large (> 2 cm) subintimal dissection was induced. None of these patients experienced any adverse clinical effects or had creatine kinase elevation. There was also no evidence of embolic events in any of our patients.

Analysis of failed procedures: In 41 patients, the occluded vessel could not be recanalized. The procedure

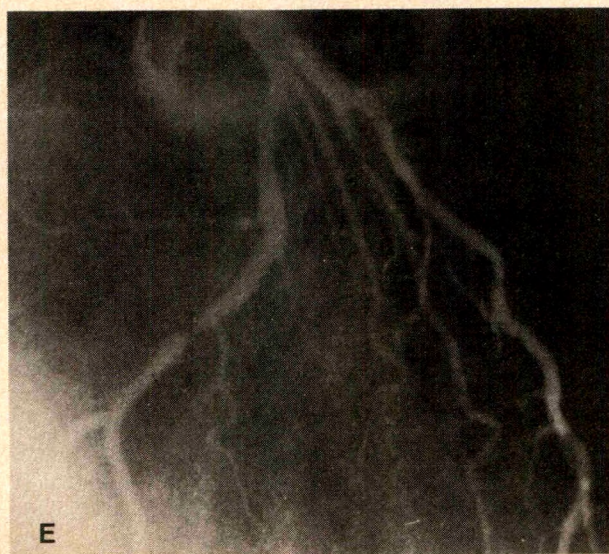
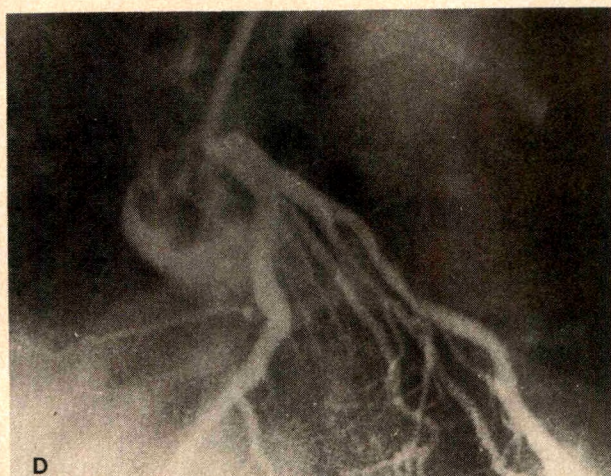
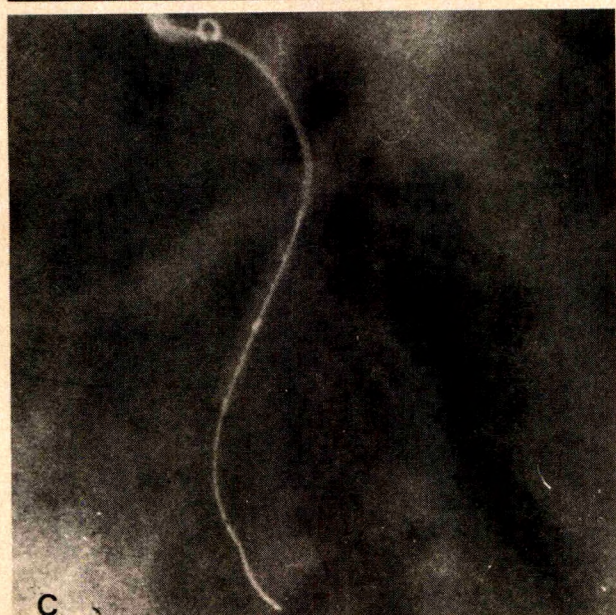


FIGURE 2. A, total occlusion of a large circumflex artery that (B) could not be crossed with a conventional guidewire. A 2.5-mm Omniflex™ passes the occlusion (C) and is inflated. D, good result with no residual stenosis. Recurrent high-grade stenosis (E) at 6-week control angiogram.

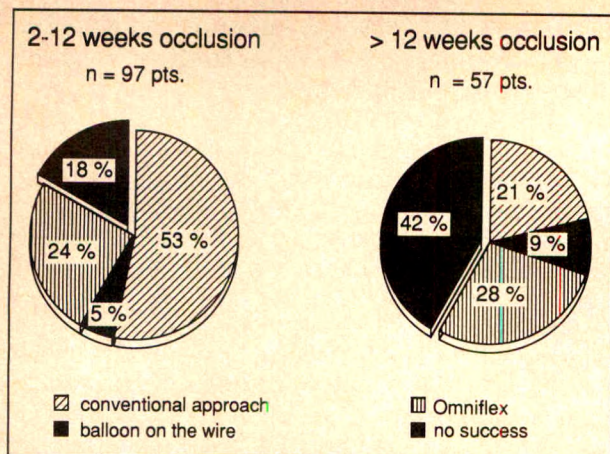


FIGURE 3. Results according to duration of occlusion.

had to be terminated because of complications in 8 patients. In the other 33, occluded vessels ($n = 14$, left anterior descending artery; $n = 5$, left circumflex artery; $n = 14$, right coronary artery) failure could be linked to the lack of a visible entrance port ($n = 8$), extreme tortuosity ($n = 8$) or, in the presence of very good local collateralization ($n = 9$), suggesting longer-lasting occlusions.

Follow-up angiographic results: Control angiograms were obtained in 52 consecutive patients after 10 ± 7 weeks after successful recanalization. In 12 patients (23%), reocclusions had occurred, and in 15 patients (29%) a restenosis $>70\%$ in diameter requiring reangioplasty had developed. In the remaining 25 patients (48%), a persistent good result was documented.

DISCUSSION

Angioplasty of total coronary occlusions has been classified by the American College of Cardiology/American Heart Association task force on the basis of the duration of the occlusion.¹ An occlusion lasting <3 months was associated with a success rate between 60 and 85%. In occlusions older than 3 months, the success was regarded to be below 60%. These figures are, however, rather poorly supported by published data.⁶⁻¹⁴

The present study confirms an 82% success rate of recanalization with angioplasty in patients with total occlusions of <12 weeks' duration. Arteries occluded from more than 3 and up to 9 months were recanalized successfully in 58% of patients. These results were achieved to a considerable degree by the use of new angioplasty devices. In occlusions older than 3 months, 37% of the lesions were managed only by the advanced, not the conventional, equipment. The complication rate was low and emergency surgery was required in only 1 patient (0.6%).

There are various limitations when comparing our results to previously published data. In early studies performed before 1986,^{7,9,11} the advanced equipment was not available. Limited experience with the new devices has been reported by others.¹⁴ The current study is the first to analyze systematically the advantages of the new equipment.

Most other studies are based on smaller numbers of patients and differ with respect to patient selection and total occlusion definition. Because fresh and functional occlusions are managed today with success rates close to those of high-grade stenoses, we included in this study only patients with "true" chronic total occlusions. The protocol of the study does not follow a randomized design but still allows us to appreciate the beneficial effect of the new equipment. We oriented our stepwise study design according to a rational clinical approach, aiming for least aggression and lowest material expense. Because most cases can be successfully managed by a conventional approach, we advise others to begin the procedure with regular guidewires.

To safely cross chronic total occlusions, one requires systems that can be pushed through the softest part of the occluding thrombus or fibrocellular material.¹⁷ High stability and exact torque control appear essential for such equipment. The Omniflex catheter currently appears to fulfill these requirements best. The recently introduced Magnum-Meier system is also very advantageous in this setting, but has not yet proven to be superior to the conventional approach.¹⁶ In some chronic occlusions there appears to be a soft, thin channel, which can be crossed only by a guidewire, but not by any over-the-wire balloons. Fixed wire systems were successful in all these lesions and should therefore be available for such cases.

Despite the improved equipment, some lesions will resist the recanalization attempt. Our results support the observation that the duration of the occlusion is a key determinant for success. Lesions older than approximately 9 to 12 months are associated with success rates that allow this procedure only in selected cases. Besides the previously discussed predictors of success, one major determinant is, obviously, the operators' experience,²⁰ as well as the primary morphologic criteria for patient selection. There is probably also a learning curve of angioplasty for total occlusions, as demonstrated for stenoses.²¹ On the other hand, increasing success rates will encourage the policy of accepting patients with unfavorable angiographic morphology.

The rate of restenoses in recanalized vessels is considered to be higher than that after angioplasty of stenosed arteries.²² Therefore, the indication of angioplasty in total occlusions has been questioned. A subset of patients in the present study underwent routine control angiography 3 months after the intervention. A complete reocclusion developed in 23% and a significant restenosis was observed in 29% of the patients at this early stage. One task of future studies is to determine the optimal interval between recanalization and control angiography in order to maintain a good long-term result.

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Low-Dose Aspirin Versus Anticoagulants for Prevention of Coronary Graft Occlusion

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The prevention of graft occlusion by aspirin (100 mg/day) or heparin followed by phenprocoumon was investigated in a randomized trial in 235 patients after aortocoronary bypass operation. Aspirin treatment started 24 hours before, and heparin 6 hours and phenprocoumon 2 days after surgery. The results of the vein graft angiography and the clinical outcome 3 months postoperatively did not differ: 22% of 218 vein graft distal anastomoses in the aspirin group and 20% of 272 in the anticoagulant group were occluded. At least 1 occluded distal anastomosis was present in 38% of 74 patients in the aspirin-treated group and in 39% of 86 in the anticoagulant group. Worst-case analysis of all randomized patients showed graft occlusions, cardiovascular complications or lost to follow-up in 42% of 122 aspirin-treated patients compared with 41% of 113 patients treated with anticoagulants. For grafts with endarterectomy the occlusion rate was lower in the aspirin (12% of 49) than in the anticoagulant (22% of 41) group ($p \leq 0.05$). Increased perioperative blood loss in the aspirin group ($1,211 \pm 814$ ml in the first 48 hours vs 874 ± 818 ml in the anticoagulant group [$p \leq 0.001$]) without a higher reoperation rate indicates effective platelet inhibition with low-dose aspirin. Because occlusion rates were equal but high in these patients with advanced stage of coronary artery disease, a combination of low-dose aspirin and anticoagulation should be investigated to reduce graft occlusion rates further.

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The success of coronary bypass operation is jeopardized by graft occlusions. They most frequently occur during the first hours and days after surgery and their origin is mainly thrombotic.¹ To prevent occlusions, antithrombotic therapy has to start early, because platelet aggregation occurs intraoperatively. Animal experiments have shown that the incidence of thrombosis in aortocoronary grafts can be decreased when platelet inhibition is begun in the first postoperative hour.² In clinical studies, a significant decrease of graft occlusions was seen in patients treated with anticoagulants or platelet inhibitors (aspirin 975 mg/day plus dipyridamole) 6 to 7 hours after surgery.^{3,4} Low-dose aspirin also resulted in a decrease in graft occlusions.⁵

Whether anticoagulation or platelet inhibition is more effective in the prevention of graft occlusions has not been clearly established. Aspirin dosage and optimal timing of treatment are disputed. Therapy initiated before surgery appears to improve the prevention of graft occlusions, but the risk of bleeding has to be evaluated. This prompted us to perform a centrally randomized, open, multicenter trial comparing the occlusion rates of grafts, bypass vessels, perioperative blood loss and clinical results in patients after coronary bypass operation treated with platelet inhibitors or anticoagulant therapy, respectively. Platelet inhibition was managed with aspirin (100 mg/day) starting 24 hours preoperatively, and anticoagulation with heparin starting 6 hours and phenprocoumon starting 2 days after surgery and continued until time of control angiography.

METHODS

Three hundred and twenty-five patients with an indication for bypass surgery, in 4 cardiology centers, were screened for the trial and 235 patients were randomized. Exclusion criteria were: gastrointestinal ulcers, bleeding disorders, allergy to aspirin or phenprocoumon, severe retinopathy, obstructive lung diseases, chronic use of analgesics or platelet inhibitors, venous thrombosis, atrial fibrillation, and additional surgery such as valve replacement. After patients gave informed consent, the randomized therapy was assigned via telex. Randomization was stratified by 4 factors: endarterectomy, ejection fraction $\leq 35\%$, single bypass, all others, and done 24 hours before surgery, because aspirin therapy had to be started immediately.

Ten days before surgery all platelet-inhibiting medication was discontinued. Heparin was not increased or given in the aspirin group. Anticoagulation was begun

TABLE I Preoperative Characteristics of the Patients

	ASA	AC
No. of patients	122	113
Mean age (yrs)	56.6 ± 7.3	55.6 ± 8.0
Weight (kg)	74.2 ± 8.9	74.9 ± 8.4
	No. (%)	No. (%)
Men	100 (82)	96 (85)
Family history of CAD	34 (28)	30 (27)
Systemic hypertension (RR ≥ 160/90)	55 (45)	61 (54)
Diabetes mellitus	19 (16)	9 (8)
Cigarette smoking (within last 5 years)	64 (52)	60 (53)
Total cholesterol (≥250 mg/dl)	50 (41)	66 (58)
Myocardial infarction (Q-wave)	59 (48)	49 (43)
Myocardial infarction (non-Q-wave)	15 (12)	16 (14)
Peripheral arterial disease	18 (15)	17 (15)
Angina related to exertion	73 (60)	82 (73)
ST-segment depression with exertion	62 (51)	65 (58)
Angina unrelated to exertion	29 (24)	20 (18)
Drugs		
Nitrates	111 (91)	97 (86)
Beta-blockers	85 (70)	78 (69)
Calcium antagonists	63 (52)	66 (58)
Digitalis	16 (13)	27 (24)
Diuretics	25 (20)	19 (17)
	Median ± SD	
Fasting plasma glucose (mg/dl)	94 ± 30	91 ± 22
Total cholesterol (mg/dl)	250 ± 52	258 ± 53
Total triglycerides (mg/dl)	177 ± 90	198 ± 85
Ejection fraction (%)	58 ± 15	57 ± 18
Severity of CAD (Gensini score)	74 ± 37	65 ± 35

AC = anticoagulation; ASA = acetylsalicylic acid; CAD = coronary artery disease; SD = standard deviation.

with heparin administered intravenously in a constant dose of 10,000 U/24 hours and phenprocoumon was added 48 hours after surgery. After reaching a prothrombin index of 30% heparin was discontinued. Only analgesics that do not interfere with platelet inhibition were administered postoperatively.

Treatment adherence: To evaluate the aspirin action, thromboxane⁵ was measured 48 hours before surgery and also at 24 hours, 48 hours, and 14 and 80 days after surgery. These tests were limited to 54 consecutive patients. Human brain thromboplastin was used in 2 of 3 prothrombin index measurements with a therapeutic range of 15 to 30% or 2.4 to 4.0 international normalized ratio. The results of laboratories using different thromboplastins were cross-checked for normal and therapeutic range with control plasma. In all patients receiving anticoagulation, the prothrombin index was measured daily for the first 10 days after surgery and then weekly thereafter.

Surgical procedure: All patients underwent operation in 1 surgical center with 5 surgeons participating. Systemic hypothermia to 28°C was used. The saphenous vein was irrigated with heparinized saline solution and slightly distended. The coronary artery lumen was measured by calibrated probes. During cardiopulmonary bypass, distal anastomoses were performed first with 7-0 prolene; proximal anastomoses were then constructed during rewarming with running 6-0 prolene. Protamin was then administered to neutralize heparin until activated clotting time was ≤120 seconds. Chest tube blood loss was recorded hourly and autotransfused

TABLE II Operative Characteristics of the Patients

	ASA	AC
No. of patients	122	113
Distal anastomoses	363	349
Distal anastomoses per patient (mean)	2.97	3.08
Single grafts	194	207
Sequential grafts	65	73
Endarterectomy	97*	57
Of the left coronary system	57	26
Of the right coronary artery	40	31
Mammary artery grafts	7	12
Operation time (min)	267 ± 73	269 ± 69
Cardiopulmonary bypass time (min)	102 ± 42	105 ± 43
Aortic cross-clamping time (min)	48 ± 22	52 ± 20
Heparin (mg)	292 ± 33	292 ± 33
Protamin (mg)	178 ± 73	175 ± 67
Activated clotting time after bypass (normal ≤120 sec)	131 ± 55	131 ± 55
Partial thromboplastin time 48 hours postoperative (normal ≤35 sec)	33 ± 11	34 ± 9
Platelet count 48 hours postop. (10 ³ /μl)	111 ± 41	126 ± 53
Hemoglobin 48 hours postop. (g/dl)	12.0 ± 1.5	12.3 ± 1.4
Reoperation	9	10
Aortic counterpulsation	9	5
Perioperative myocardial infarction	16	15
New Q waves or loss of R waves		

* p ≤ 0.05.

Values are expressed as mean ± standard deviation. postop. = postoperatively; other abbreviations as in Table I.

in most patients. Blood transfusion requirements during and after operation were tabulated for each patient.

Control angiography: A control angiography was planned at 8 to 12 weeks after surgery. The grafts were opacified selectively in ≥2 projections. An additional biplane aortic root angiography was performed if a bypass could not be identified. The data were analyzed centrally and blindly by 3 independent investigators. Grafts (distal anastomoses) fully visualized to supply the distal artery during selective injection were called "patent"; otherwise, they were considered occluded. Each distal anastomosis was calculated separately. If there was a suspicion, deep vein thrombosis was diagnosed by angiography and pulmonary embolism by scintigraphy.

Data analysis and statistics: After data recording, verification of errors and comparison of the baseline characteristics, statistical analysis was performed using the intention-to-treat strategy. An α error level of 0.05 was chosen. The trial protocol had been accepted by the ethics committee of the University of Munich.

RESULTS

Randomization led to comparable treatment groups (Tables I and II). The intraoperative situation, however, made changes concerning the stratum endarterectomy subsequently necessary. Each of the participating surgeons operated on a comparable number of patients receiving both therapies. Sixty-one percent (74 of 122) of the aspirin-treated patients and 76% (86 of 113) of the phenprocoumon-treated patients underwent control angiography performed 82 ± 53 days (aspirin group) and 81 ± 46 days after surgery, respectively (phenprocoumon group). The consent to the control angiography

TABLE III Evaluation of All Randomized Patients

	ASA	AC
No. of patients	122	113
Patients with ≥ 1 distal anastomoses occluded at vein-graft angiography	28	34
Patients without vein-graft angiography		
With angina pectoris or new infarction	3	2
With other cardiovascular complication	12	6
Breakup (intolerance to ASA, bleeding complication, indication for anticoagulation in ASA group)	5	3
Dropout (lost to follow-up)	3	1
Worst case analysis: graft occlusion, cardiovascular event, breakup, dropout	51 (42%)	46 (41%)

Abbreviations as in Table I.

was withdrawn by 28 patients in the aspirin group and 17 patients in the phenprocoumon group. Of these patients 25 treated with aspirin and 15 with phenprocoumon were free of symptoms.

The graft occlusion rate did not differ significantly in both groups. Twenty-two percent (47 of 218) of distal anastomoses were occluded in the aspirin group compared with 20% (55 of 272) in the phenprocoumon group. In the aspirin group, 38% (28 of 74) of the patients had at least 1 bypass occluded, whereas the percentage in the anticoagulant group was 39% (34 of 86) (Figure 1).

When patients without control angiography were added to the analysis, clinical end points, breakups, dropouts or graft occlusions occurred in 42% (51 of 122) of patients in the aspirin group and in 41% (46 of 113) of patients in the anticoagulant group (Table III).

With regard to the different vessel areas and diameters, no significant difference in the occlusion rates was found (Table IV). The occlusion rate of bypassed stenoses was 19% (35 of 187) in the anticoagulant group compared with 25% (43 of 169) in the aspirin group (difference not significant). At the time of control angiography, 66% of aspirin-treated patients no longer had angina and 26% had improvement in their condition. In

TABLE IV Relative Frequency of Vein Graft Occlusions According to Location, Vessel Diameter, Type of Graft

	ASA No. (%)	AC No. (%)
Coronary artery grafted		
Left anterior descending	9/68 (13)	10/80 (12)
Diagonal branch	3/14 (21)	7/31 (23)
Left circumflex	27/77 (35)	20/84 (24)
Right	8/59 (14)	18/77 (23)
Coronary diameter		
<1.5 mm	30/124 (24)	40/177 (23)
≥ 1.5 mm	15/68 (22)	13/61 (21)
Type of graft		
Single graft	32/123 (26)	33/166 (20)
Sequential graft	9/43 (21)	12/58 (21)
Endarterectomy*	6/49 (12)	9/41 (22)
Mammary artery	-/3	1/7

* $p \leq 0.05$.

Abbreviations as in Table I.

the anticoagulant group the figures were 68 and 26%, respectively. In contrast to these results, the occlusion rate of endarterectomized vessels was lower with aspirin (12%, 6 of 49) than with anticoagulant therapy (22%, 9 of 41) (Table IV).

The mean blood loss via pericardial drainages in the aspirin group was $1,211 \pm 814$ ml compared with 874 ± 818 ml in the anticoagulant group ($p \leq 0.001$). Correspondingly, the mean transfusion volume was increased by 343 ml ($p \leq 0.001$) (Figure 2).

Complications: Six patients in the aspirin and 1 patient in the anticoagulant group died from perioperative myocardial infarction; 1 patient taking aspirin had a cerebral embolus and another had septic shock after congestive heart failure. In the anticoagulant group, 1 patient died from acute left ventricular failure after aneurysmectomy. This patient should not have been randomized. From each group, 1 patient died suddenly of cardiac causes during the further course of the study. The difference in the number of casualties in both groups was not statistically significant. Endarterectomy

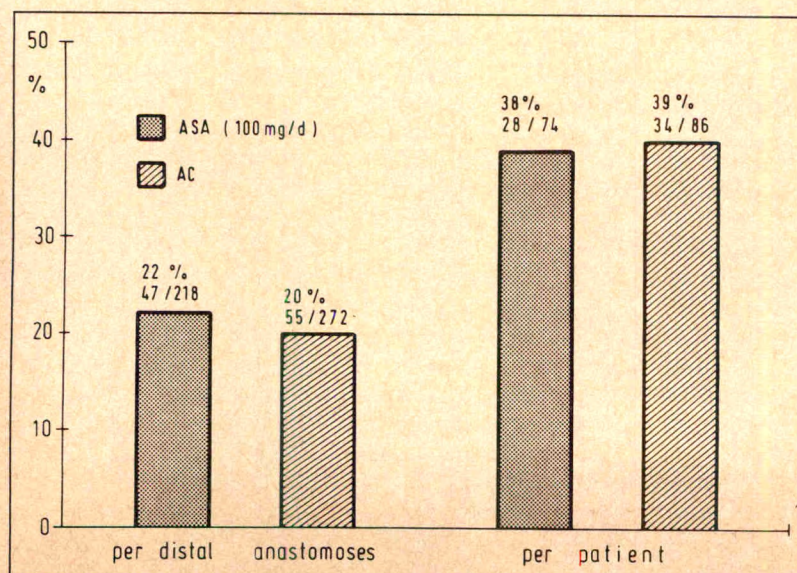


FIGURE 1. Occlusion rates of vein grafts. The rates refer to all vein graft distal anastomoses in patients who had vein graft angiography and are expressed as (%) of occluded distal anastomoses and proportion of patients with at least 1 occlusion. AC = anticoagulant therapy; ASA = acetylsalicylic acid.

proved to be a particular risk factor: 7 of the 11 casualties after surgery and 22 of the 31 patients with perioperative myocardial infarction had undergone an endarterectomy. Further nonfatal complications are listed in Table V.

Treatment adherence: Platelet thromboxane formation was completely suppressed in 95% of all patients tested. In the anticoagulant group, heparin was given for 5 ± 2 (2 to 22) days (mean prothrombin index after 6 to 7 days was $32 \pm 17\%$, and after 9 to 10 days $22 \pm 9\%$). Routine measurements in the anticoagulated group showed a prothrombin index $\leq 30\%$ in 78% of the patients. Patients with at least 1 bypass occlusion did not have higher levels of the prothrombin index than those with no occlusion. Cross-checks with identical reference plasmas corresponded well in 9 of 10 checks.

DISCUSSION

Graft occlusion rate: When treatment with low-dose aspirin or anticoagulants was compared in 235 patients after aortocoronary bypass operation, no significant difference favoring either form of therapy was seen. The occlusion rate of distal anastomoses, the major end point, was 21.6% with aspirin and 20.2% with anticoagulant therapy. The 95% confidence interval for this difference is $1.4 \pm 7.2\%$; this supports the conclusion that there is no clinically relevant difference in bypass occlusion rates between aspirin and anticoagulants. This is supported by 2 other studies after bypass surgery with platelet inhibition versus anticoagulation showing occlusion rates of 16% with ticlopidin and 18% with acenocoumarol,⁶ and 20% with aspirin plus dipyridamole versus 16% with phenprocoumon.⁷ The significant lower occlusion rate among patients who underwent endarterectomy and were treated with aspirin rather than anticoagulants confirms reports indicating that platelet inhibition after endarterectomy improves patency.⁸

The bypass occlusion rate (20 and 22%, respectively) of distal anastomoses is higher than the numbers reported by other investigators,^{3,4,6,8-17} but is supported by a recent study (16 to 20% occlusion rate).⁷ In contrast to

TABLE V Nonfatal Complications*

	ASA (no.)	AC (no.)
Ischemic stroke	2	2
Hemorrhagic stroke	—	—
Pulmonary embolism	2	—
Deep venous thrombosis	1	—
Gastrointestinal bleeding (requiring ≥ 2 units of blood)	1	2
Macrohematuria	3	7
Pericardial effusion (≥ 0.5 cm diastolic)	14	23
Pericardial tamponade	—	3
Atrial fibrillation	48	34

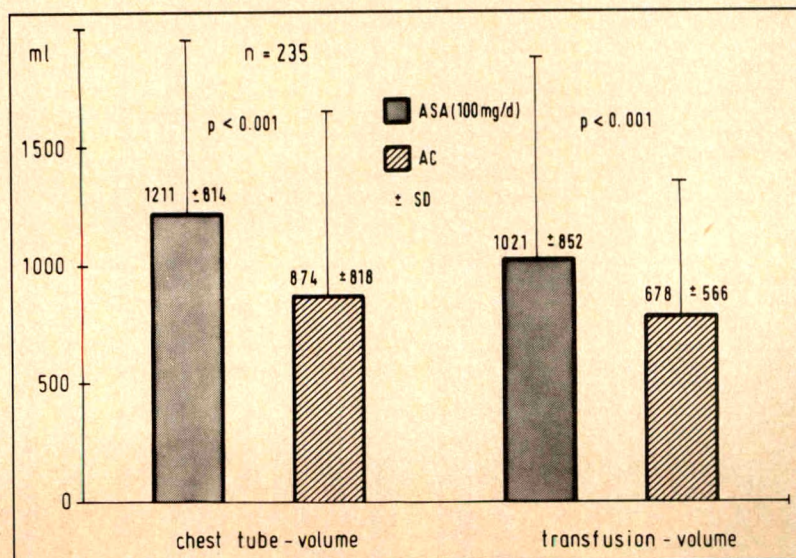
* Multiple complications possible.
Abbreviations as in Table I.

most studies, patients with a higher risk for occlusion like diabetes mellitus, unstable angina, or necessity for endarterectomy were included in our study, as were patients who underwent emergency operation. They represent about 70% of all patients undergoing coronary artery surgery at the participating cardiology centers during the study period compared with only 21% in the Veterans Administration Cooperative Study.¹⁷ The rate of control angiography was 68% overall, which was influenced in part, by the patients' symptoms, thus preselecting patients with a higher bypass occlusion rate for the control angiography. Overall, the high occlusion rates reflect the advanced stage of coronary artery disease in these patients as is outlined by the high number of endarterectomies (22% of all grafts compared with 1.7%¹⁷).

Complications: Anticoagulation increased the risk of perioperative pericardial effusions and therefore also the risk of tamponades. Severe bleeding was rare in both groups. Gastrointestinal side effects did not occur with the low dosage of aspirin used.

The frequency of perioperative infarctions (13%) and mortality (3.8%) agrees with results reported in other studies with a comparable number of endarterec-

FIGURE 2. Chest tube drainage and blood transfusion during the first 48 hours after operation. SD = standard deviation; other abbreviations as in Figure 1.



tomies, especially to the left coronary artery.^{8,18} Mortality in patients without endarterectomy was <1% as also described by other workers.^{3,4} Detailed analyses did not indicate a correlation between study medication and casualties.

Timing of therapy: An early postoperative onset of therapy is of major importance for successful prevention of bypass occlusion.^{3,13} Starting therapy 3 to 6 days after surgery has added to the failure of a number of studies concerning antithrombotic therapy after bypass operation.¹⁴⁻¹⁶ Further improvement in prevention of graft occlusion seemed to be made possible by a preoperative start of platelet inhibition, but this resulted in increased blood loss. Whether it improves patency rates has not yet been demonstrated.

Aspirin dosage: Low-dose aspirin is at least equally, possibly even more potent than high-dose aspirin, because aspirin in low doses reduces thromboxane A₂ production more effectively than the genesis of prostacyclin.^{19,20} This fact might enhance the platelet-inhibiting effect.^{21,22} This so-called pseudoselective inhibition of thromboxane persists in arteriosclerotic patients and during long-term use.²³⁻²⁵ In clinical studies, the anti-thrombotic effect could not be increased by higher dosages or by adding dipyridamole.^{9,17}

Reduction of myocardial infarction and death was demonstrated with low-dose aspirin in unstable angina, after thrombolysis in acute myocardial infarction and in a primary prevention trial.²⁶⁻²⁸ The low dosage (e.g., 100 mg/day) should be given, because adverse effects are dose dependent but antiplatelet activity is not. A comparable increase in blood loss, particularly linked to a higher incidence of reoperation was found when a higher dosage of aspirin was administered preoperatively.^{16,17}

Because occlusion rates were equal but high in these patients with advanced coronary artery disease, a combination of low-dose aspirin and anticoagulants should be investigated to reduce graft occlusion rates further.

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Arterial Vasodilator Effects of the Dihydropyridine Calcium Antagonist Amlodipine Alone and in Combination with Verapamil in Systemic Hypertension

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The arterial vasodilator properties of the dihydropyridine calcium antagonist amlodipine were compared with the effects of vascular muscle cyclic guanosine monophosphate production by sodium nitroprusside and with the effects of a combined infusion of amlodipine and the nondihydropyridine calcium antagonist verapamil in 8 untreated patients with primary hypertension. Arterial vasodilation was assessed by measurement of changes of forearm blood flow by mercury in Silastic strain-gauge plethysmography during brachial artery drug infusions. Forearm blood flow increased during amlodipine infusions (0.4 to $45 \mu\text{g}/\text{min}/100 \text{ ml}$ forearm tissue) from 2.9 ± 1.7 to a maximum of $23.6 \pm 7.6 \text{ ml}/\text{min}/100 \text{ ml}$ (687%), while sodium nitroprusside caused an increase from 3.0 ± 1.8 to $16.2 \pm 5.4 \text{ ml}/\text{min}/100 \text{ ml}$ (449%), attesting to the importance of transmembrane calcium influx for the maintenance of vascular tone. The addition of verapamil $40 \mu\text{g}/\text{min}/100 \text{ ml}$ to an infusion of amlodipine $44.5 \mu\text{g}/\text{min}/100 \text{ ml}$ resulted in a further increase of forearm blood flow, from 23.6 ± 7.6 to $34.4 \pm 9.8 \text{ ml}/\text{min}/100 \text{ ml}$ ($p < 0.05$). The precise mechanisms of this finding have yet to be elucidated but may be due to interactions of the effects of the binding of these 2 chemically and pharmacologically different calcium antagonists to distinct binding sites at calcium channels. The clinical relevance of this observation for the treatment of coronary artery disease and systemic hypertension needs further study.

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Calcium antagonists reduce calcium influx into vascular muscle cells and therefore are potent arterial vasodilators.¹⁻³ To block sarcolemmal calcium flux into the cell, calcium antagonists interact in a specific but not yet completely understood way with the structure of calcium channels.⁴ It has been shown that the 3 principal classes of calcium antagonists (e.g., dihydropyridine calcium antagonists, verapamil and diltiazem-like compounds) bind to different sites at calcium channels.⁵⁻⁷ However, it is not known whether blockade by 1 type of drug leads to maximal reduction of calcium influx or whether a combination of 2 different calcium antagonists results in a greater inhibition of calcium influx and, therefore, vasodilatation. Clinical studies have shown that the combination of 2 calcium antagonists from 2 different classes produced greater antiischemic effects in patients with vasospastic and effort angina pectoris.⁸⁻¹¹ Although the underlying mechanisms for this additional clinical effect are unknown, the possibility exists that the vasodilating effects of both drugs are additive to each other. To investigate this contention, we studied the vasodilating effects of 2 calcium antagonists from 2 different classes (e.g., the dihydropyridine amlodipine and the phenylalkylamine-derivative verapamil) using the model of intraarterial drug infusion into the human forearm. Furthermore, we compared the vasodilator effects of calcium channel blockade with the effects of sodium nitroprusside, which stimulates production of vascular cyclic guanosine monophosphate.¹²

METHODS

Patients: The vasodilator activity of amlodipine was investigated in 8 patients (5 men and 3 women, aged 44 to 59 [mean \pm standard deviation 51] years) with mild to moderate hypertension who were either previously untreated or had been taken off any medication for ≥ 2 weeks. Casual sitting blood pressure without therapy was $172 \pm 6/108 \pm 3 \text{ mm Hg}$. The study protocol was approved by the hospital ethics committee and all patients gave informed consent.

Forearm blood flow measurements: The model of intraarterial drug infusion into the forearm was used to assess the drug's effects on vascular resistance independent of systemic hemodynamic effects and possible counterregulatory reflexly mediated hemodynamic changes. Details of the procedure have been described.³ In short, the brachial artery of the nondominant arm is

cannulated for direct measurement of blood pressure and intraarterial drug infusion. Forearm blood flow was measured by venous occlusion plethysmography, with the hand excluded from the circulation during measurements. Four to 6 measurements were recorded every minute and averaged for analysis.

Study protocol: Forearm blood flow was measured at rest and during the third minute of an infusion of sodium nitroprusside ($0.6 \mu\text{g}/\text{min}/100 \text{ ml}$ forearm tissue) delivered by a constant-speed infusion pump. The dose was chosen based on previous findings of maximal regional vasodilatation without significant systemic hemodynamic effects.¹³ After forearm blood flow had returned to control values, ascending dosages of amlodipine ($0.4, 0.8, 1.6, 3, 6, 12, 22.5$ and $45 \mu\text{g}/\text{min}/100 \text{ ml}$ forearm tissue) were infused; forearm blood flow was measured in the third minute of each infusion. Because amlodipine has a long duration of action,^{14,15} it was found impractical to wait for forearm blood flow to return to control values after amlodipine infusions. Therefore, after the last amlodipine infusion, verapamil was infused in a dose of $40 \mu\text{g}/\text{min}/100 \text{ ml}$ in combination with amlodipine $44.5 \mu\text{g}/\text{min}/100 \text{ ml}$ over 3 minutes. Forearm blood flow was measured in the third minute of the combined infusion. The dose of verapamil was chosen based on a previous study that demonstrated that this dose was half the dose required for maximal

regional vasodilatation (e.g., an increase of forearm blood flow without systemic hemodynamic effects).¹⁶ The time schedule of drug-effect assessments was based on the finding that, for both compounds, forearm blood flow increased rapidly in the first minute of drug infusion and was constant from the second minute onwards.

Calculations: All values are presented as means \pm standard deviation as an index of dispersion. Forearm vascular resistance was calculated by dividing mean arterial pressure and forearm blood flow (expressed in units). Student's paired *t* test was used for assessment of differences between the various interventions.

RESULTS

There were no significant changes in blood pressure or heart rate after any of the intraarterial infusions, indicating a lack of systemic effects of the intraarterial infusion regimens. Thus, changes of forearm hemodynamics can be ascribed only to the drug's peripheral vascular actions.

The results of the intraarterial infusions of amlodipine on forearm blood flow are shown in Figure 1. Amlodipine increased forearm blood flow significantly and dose dependently from $2.9 \pm 1.7 \text{ ml}/\text{min}/100 \text{ ml}$ during control conditions to $23.6 \pm 7.6 \text{ ml}/\text{min}/100 \text{ ml}$ during infusion of the highest dosage. Accordingly, calculated forearm vascular resistance decreased by a

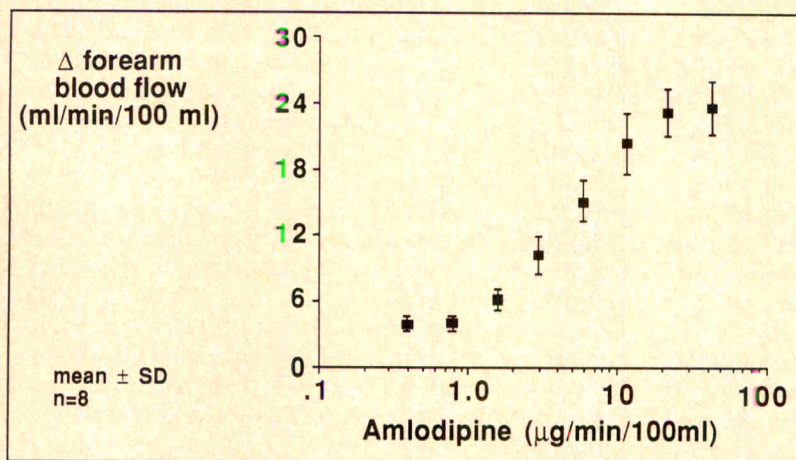


FIGURE 1. Changes of forearm blood flow during graded brachial artery infusions of amlodipine in 8 patients with primary hypertension. Values are means \pm standard deviation (SD).

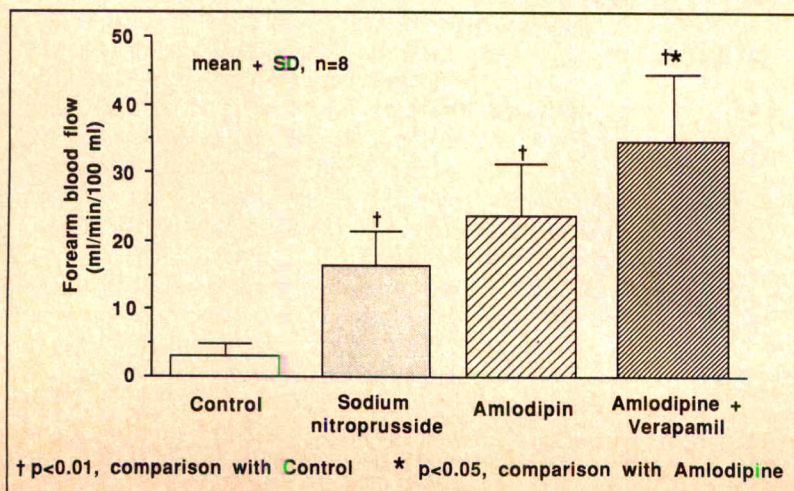


FIGURE 2. Comparison of vasodilator effects of sodium nitroprusside, amlodipine and a combination of amlodipine and verapamil in 8 patients with primary hypertension. Values are means \pm standard deviation (SD).

maximum of $87.5 \pm 6.7\%$. There was no additional increase in forearm blood flow or decrease of forearm vascular resistance from the second highest to the highest dose, indicating that the maximal vasodilator effect of amlodipine was achieved with the infusion regimen. The comparative vasodilator effects of sodium nitroprusside, amlodipine and the combination of amlodipine and verapamil are depicted in Figure 2. Whereas sodium nitroprusside increased forearm blood flow from 3.0 ± 1.8 to 16.2 ± 5.4 ml/min/100 ml (449%), amlodipine increased flow to a significantly greater extent (23.6 ± 7.6 ml/min/100 ml [687%], $p < 0.01$). Addition of verapamil ($40 \mu\text{g}/\text{min}/100$ ml) to amlodipine ($45 \mu\text{g}/\text{min}/100$ ml) increased forearm blood flow significantly further, to above the level achieved with amlodipine alone (34.4 ± 9.8 vs 23.6 ± 7.6 ml/min/100 ml, $p < 0.05$). No relation was found between increases of forearm blood flow in response to any drug or drug combination and blood pressure.

DISCUSSION

Our results demonstrate that amlodipine, like nifedipine,³ verapamil,¹⁶ or diltiazem,¹⁷ is a powerful arterial vasodilator, leading to greater vasodilatation as compared to sodium nitroprusside, which acts through elevation of cytosolic cyclic guanosine monophosphate levels. Although we did not construct a dose-response curve for sodium nitroprusside, the dose used has been shown to result in maximal forearm vasodilatation.^{13,18} Thus, this finding underscores the importance of transmembrane calcium influx for the maintenance of vascular tone, particularly in hypertensive patients in whom calcium-influx-dependent vasoconstriction is greater than in normotensive subjects.^{1,2} Accordingly, a reduction of this component of vascular tone has been advocated as a physiologic and rational way to normalize blood pressure at rest,^{3,16,17} during physical exercise^{19,20} and mental stress.²¹ The peripheral and coronary vasodilator activity of these compounds also play a major role in their antiischemic effects.²²

One interesting observation is the finding that the combination of 2 calcium antagonists from different classes leads to greater vasodilatation than amlodipine alone. There is no ready explanation of this finding. However, at least 2 different molecular binding sites have been demonstrated (e.g., for dihydropyridine, verapamil and diltiazem-type calcium antagonists).⁵⁻⁷ Although the exact interactions between these structures are not completely understood, there seems to be a closer similarity, if not an identity, between the verapamil and diltiazem binding sites than between either the verapamil and dihydropyridine or the diltiazem and dihydropyridine binding sites.⁷ Thus, effects of a dihydropyridine in combination with a nondihydropyridine calcium antagonist might be expected, on theoretical grounds, to be more pronounced than the combination of verapamil and, for example, diltiazem. Our data with combined infusions of amlodipine and verapamil are compatible with this hypothesis.

The choice of the verapamil dosage ($40 \mu\text{g}/\text{min}/100$ ml) used for the combined intraarterial infusion needs

comment. This dose has been previously shown to be half the dose required for maximal vasodilatation in the forearm model.¹ Thus, a greater dose of verapamil might have caused even greater vasodilatation in combination with amlodipine than the submaximal dose used in our study.

There are limited clinical data showing that the combination of the dihydropyridine calcium antagonist nifedipine with diltiazem is more effective in the treatment of vasospastic^{8,9} or effort angina pectoris^{10,11} than either drug alone. Although the antiischemic effect of systemically administered calcium antagonists in effort angina pectoris entails more than peripheral vasodilatation, the additive effects in vasospastic angina might be taken as evidence for an additive coronary vasodilator effect, similar to the one observed in the forearm circulation in our study.

In all, our data indicate that the dihydropyridine calcium antagonist amlodipine is in itself a potent vasodilator of human resistance vessels. The additional vasodilatation combined with verapamil suggests that co-administration of nondihydropyridine and dihydropyridine calcium antagonists may be useful in certain situations. However, more data are needed to document the mechanisms of interaction, the efficacy, tolerability, and, in particular, the safety of systemic applications of such combinations.

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Left Ventricular Filling Impairment in Asymptomatic Chronic Alcoholics

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Systolic left ventricular dysfunction is relatively common in even asymptomatic alcoholics, but whether diastolic function is also altered is much less well-studied. We used M-mode and Doppler echocardiography to study left ventricular size, mass, systolic function and diastolic filling in 32 alcoholics free of clinically detectable heart disease and in 15 healthy control subjects. Left ventricular mass index and posterior wall thickness were higher in alcoholics than in controls, but there was no statistically significant difference either in end-diastolic size or in systolic ventricular function. More abnormalities were found in the Doppler indexes of diastolic function, however. The alcoholics had a prolonged relaxation time (200 ± 6 vs 184 ± 5 ms [mean \pm standard error], $p < 0.05$), a decreased peak early diastolic velocity (52 ± 2 vs 60 ± 3 cm/s, $p < 0.05$), a slower acceleration of the early flow (410 ± 18 vs 552 ± 43 cm/s², $p < 0.01$), and a higher atrial-to-early peak velocity ratio (0.74 ± 0.04 vs 0.60 ± 0.05 , $p < 0.05$). This pattern of changes suggests a primary abnormality in the relaxation of the left ventricle. In multivariate analyses, the abnormalities in the Doppler indexes were independent of the duration of alcoholism, the quantity of the most recent ethanol exposure and the increased mass of the left ventricle. Impaired early filling of the left ventricle due to delayed relaxation is common in asymptomatic alcoholics and may in fact be the earliest functional sign of pre-clinical alcoholic cardiomyopathy.

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The preclinical form of alcoholic cardiomyopathy is characterized by left ventricular hypertrophy, mild systolic dysfunction, poor response to an afterload challenge and a propensity for arrhythmias.¹⁻⁴ Whether the diastolic heart function is also altered is much less studied, although both impaired and well-maintained left ventricular filling have been reported.⁵⁻⁷ Yet, in experimental animals, impaired left ventricular compliance has been reported to be the first symptom of alcohol's chronic cardiotoxicity.⁸ We have shown that, apart from its preload decreasing effect, alcohol has little or no acute influence on left ventricular filling in healthy nonalcoholic subjects.⁹ In the present study we examined diastolic function by Doppler echocardiography in alcoholics without clinically detectable heart disease. Our aim was, first, to compare alcoholics with healthy subjects and, second, to examine by methods of multivariate analysis whether the diastolic ventricular function in alcoholics is dependent on the duration of heavy drinking or on the quantity of the most recent ethanol exposure.

METHODS

Alcoholics: Thirty-seven alcoholics were consecutively hospitalized for detoxification and research purposes. They were initially admitted either to a municipal detoxification center or to a nearby psychiatric unit and were then referred to our hospital if they consented to participate in research projects necessitating a 2- to 6-week stay in a medical ward. For inclusion into the present investigation, they also had to be free of history, symptoms and signs of any manifest cardiovascular or metabolic disease, and a Doppler ultrasound study of mitral flow had to be technically possible. Historical hangover-related transient palpitation or chest pain unlike angina pectoris was not used as an exclusion criterion. The final study group comprised 32 male alcoholics aged 30 to 55 years; their mean age (\pm standard deviation) was 39 ± 7 years.

Procedures: The day after admission the patients underwent routine laboratory tests to study, among other parameters, blood count, serum electrolytes (including magnesium and calcium) and liver enzymes. A 12-lead electrocardiogram was recorded at a speed of 50 mm/s, and a chest radiogram was also recorded.

The studies in the cardiovascular laboratory were made after symptoms of withdrawal from alcohol were over, a median of 13 days after the last drink (range 4 to 55). The patients were examined clinically and questioned carefully regarding their drinking habits, past and present. The total duration (years) of heavy

TABLE I Intraobserver and Interstudy Repeatability of Doppler Echocardiographic Indexes of Left Ventricular Diastolic Function

Index	Root-Mean-Square Difference*	
	Intraobserver (n = 10)	Interstudy (n = 5)
Relaxation time (ms)	11	10
Peak early diastolic velocity (cm/s)	1.6	4.5
Peak atrial velocity (cm/s)	1.6	3.8
Atrial-to-early peak velocity ratio	0.02	0.05
Acceleration of early flow (cm/s ²)	68	114
Deceleration of early flow (cm/s ²)	39	64
Peak filling rate (s ⁻¹)	0.08	0.4

* Represents standard deviation of the difference between 2 measurements of the same tracing (intraobserver repeatability) or between 2 separate recordings of the same patient (interstudy repeatability).¹⁴

consumption and the length (weeks) of the last drinking period were recorded separately. The types and amounts of all alcoholic beverages typically consumed in 1 day were noted, converted into grams of absolute ethanol and added up to produce an estimate of daily consumption. The quantity of recent ethanol exposure (g/kg) was calculated by multiplying the estimate of daily ethanol consumption by the number of days in the last drinking period and dividing the product by body weight. The length of smoking history was also recorded, along with the number of cigarettes currently smoked per day.

After the clinical assessment and interview, patients underwent a combined 2-dimensional and M-mode echocardiographic study of the left ventricle and a pulsed Doppler examination of the transmitral flow. Blood pressure was measured using a calibrated sphygmomanometer and the cuff method. All cardiovascular studies were made ≥ 2 hours after the last meal.

Imaging echocardiography: The cardiac imaging studies were performed using a Toshiba SSH-60A echocardiograph equipped with a 3.7-MHz phased-array transducer and a strip-chart recorder. A 2-dimensional evaluation was made first to rule out gross segmental abnormalities of left ventricular function. A standard M-mode recording of the left ventricle was then performed by methods described in detail previously¹⁰; the recording speed was 50 mm/s. The strips were coded and later analyzed blindly using an x-y digitizer and computer assistance. The following left ventricular measurements were made, as recently described¹¹: end-diastolic diameter, fractional shortening, mass, septal thickness, posterior wall thickness, and thickness-to-radius ratio. The end-diastolic diameter and mass of the left ventricle were indexed by dividing with body area. All measurements were averaged over 5 cardiac cycles.

Doppler echocardiography: Pulsed Doppler recordings of the transmitral flow were made with a Toshiba SDS-60A Doppler unit and a 2.5-MHz transducer. The studies were performed with the subject in left lateral recumbency and using an apical transducer position. The ultrasound beam was directed parallel to the assumed left ventricular inflow and the sample volume

was placed between the mitral valve leaflets, just distal to the mitral annulus. The position and size of the sample volume were adjusted to obtain maximal and clearly defined velocity wave forms. No angle correction was applied. The velocity spectra were recorded during quiet respiration, together with an electrocardiogram and an external phonocardiogram at a paper speed of 50 mm/s.

The midpoints of the darkest portions of the Doppler velocity wave forms were traced on the digitizing tablet to calculate the peak late (atrial) and early diastolic flow velocities, their arithmetic ratio and the ratio of the peak early diastolic velocity to the total diastolic time-velocity integral (i.e., the normalized peak filling rate according to Bowman et al).¹² The relaxation time was measured from the beginning of the second heart sound on the phonocardiogram to the point of the peak early diastolic velocity; this time covers the period of relaxation more completely than the duration of the mere isometric relaxation.¹³ The acceleration and deceleration of the early flow were determined by fitting straight lines to the upslope and the initial downslope, respectively, of the early velocity wave. All measurements were averaged over 5 cardiac cycles.

Reproducibility: To assess the variation in measuring the Doppler tracings (intraobserver repeatability), the recordings of 10 subjects (6 alcoholics and 4 control subjects) were blindly digitized twice by the same investigator at an interval of several weeks. In addition, to characterize and quantify the variation between examinations (interstudy repeatability), 5 control subjects underwent 2 recordings of transmitral flow under identical conditions at an interval of 1 hour. The strips were analyzed blindly as mentioned. Both intraobserver and interstudy repeatability were assessed as suggested by Bland and Altman,¹⁴ by taking square roots of the mean square differences between the respective 2 examinations. The results are summarized in Table I; they compare favorably with the reproducibility data reported by other investigators.¹⁵

Control subjects: For a control group, we studied 15 healthy male volunteers aged 34 to 52 years (mean 40 ± 5). They were only occasional drinkers and free of cardiovascular disease on the basis of history, clinical examination and 12-lead electrocardiography. All underwent the aforementioned 2-dimensional and M-mode echocardiographic examination of the left ventricle and pulsed Doppler study of the transmitral flow.

Statistical analysis: Student's nonpaired *t* test was used to compare the cardiovascular measurements between alcoholics and healthy subjects. Multiple linear regression (BMDP software) was used to assess among the alcoholics the dependency of the Doppler measurements on the details of the drinking history and on several confounding cardiac or noncardiac factors. All tests were 2-tailed and *p* values <0.05 were considered statistically significant.

RESULTS

Description of the alcoholics: The majority of the 32 alcoholics were episodic drinkers. The overall duration of heavy alcohol use ranged from 1 to 24 years (median

TABLE II M-Mode Echocardiographic Left Ventricular Measurements in Alcoholics and Control Subjects

Measurement	Alcoholics (n = 30)	Control Subjects (n = 15)	p Value*
End-diastolic diameter index (mm/m ²)	25.9 ± 0.5	26.0 ± 0.6	0.88
Fractional shortening (%)	29.1 ± 0.9	31.7 ± 1.0	0.07
Septal thickness (mm)	11.5 ± 0.4	10.7 ± 0.4	0.12
Posterior wall thickness (mm)	11.1 ± 0.4	9.7 ± 0.3	0.01
Thickness-to-radius ratio	0.46 ± 0.02	0.41 ± 0.02	0.06
Mass index (g/m ²)	86 ± 3	77 ± 2	0.01

* Student's *t* test.
Values are mean ± standard error.

11) and the length of the last uninterrupted drinking period from 0.5 to 250 weeks (median 6.5). The amount of daily ethanol consumption varied from 90 to 460 g (median 297) and the total quantity of recent uninterrupted use from 9 to 3,971 g/kg body weight (median 196). The length of the smoking history ranged from 0 to 33 years (median 20) and the number of cigarettes consumed daily from 0 to 60 (median 25). Only 1 alcoholic was a nonsmoker.

The 12-lead electrocardiograms revealed a voltage sum (SV₁ + RV₅) >3.5 mV in 10 alcoholics (32%) of whom 5 were aged >40 years. On chest radiography, 13 (41%) had a heart volume >500 ml/m² of body area but none had any degree of pulmonary venous congestion. At least 1 of the 3 measured liver enzymes (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase) was elevated in 17 alcoholics (53%) and all 3 were elevated in 4 (13%). Serum potassium and magnesium were each abnormally low in 2 subjects (6%). Serum calcium was normal in all.

Comparisons between alcoholics and healthy subjects: There were no statistically significant differences in heart rate or blood pressure between the alcoholics and the healthy subjects: Heart rate was 66 ± 2 beats/min in the former group and 65 ± 3 beats/min in the latter, systolic blood pressure measured 118 ± 2 mm Hg in alcoholics and 124 ± 2 mm Hg in controls, and the respective readings for diastolic blood pressure were 76 ± 2 mm Hg and 80 ± 2 mm Hg.

Table II summarizes the M-mode echocardiographic measurements and Table III gives the results of the Doppler measurements in alcoholics and control subjects. Compared with healthy subjects, alcoholics had a prolonged relaxation time, lower acceleration and peak velocity of the early flow, and a higher atrial-to-early peak velocity ratio; together, these changes suggest impaired early filling of the left ventricle. Although the group differences were quite clear, all the foregoing measurements were within the 95% confidence intervals of the data obtained in our nonalcoholic subjects in 13 of the 32 alcoholics.

Multiple regression analyses of the Doppler data in alcoholics: Linear regression models, with each of the Doppler measurements considered separately as the dependent variable, and the duration of chronic heavy drinking, quantity of recent ethanol use, age, heart rate,

TABLE III Doppler Indexes of Left Ventricular Diastolic Function in Alcoholics and Control Subjects

Index	Alcoholics (n = 32)	Control Subjects (n = 15)	p Value*
Relaxation time (ms)	200 ± 6	184 ± 5	0.04
Peak early diastolic velocity (cm/s)	52 ± 2	60 ± 3	0.02
Peak atrial velocity (cm/s)	37 ± 2	36 ± 2	0.72
Atrial-to-early peak velocity ratio	0.74 ± 0.04	0.60 ± 0.05	0.04
Acceleration of early flow (cm/s ²)	410 ± 18	552 ± 43	0.007
Deceleration of early flow (cm/s ²)	-342 ± 17	-361 ± 17	0.42
Peak filling rate (s ⁻¹)	4.2 ± 0.09	4.4 ± 0.12	0.23

* Student's *t* test.
Values are mean ± standard error.

number of cigarettes consumed daily and the thickness-to-radius ratio considered as independent variables, were fitted to the data using the least-squares method. Left ventricular mass index was included in the model interchangeably with the thickness-to-radius ratio. The fit was statistically significant for the peak atrial velocity (F = 2.9, *p* < 0.05) and the atrial-to-early peak velocity ratio (F = 6.4, *p* < 0.001). In both instances this was due to the effects of age and heart rate on the Doppler indexes. Neither the duration of heavy drinking, the quantity of recent uninterrupted ethanol use, nor any other factor besides age and heart rate proved to be significant determinants of the indexes of diastolic function among the alcoholics.

DISCUSSION

The results of our study indicate that asymptomatic chronic alcoholics frequently have subnormal diastolic function in addition to increased wall thickness and mass of the left ventricle. Subtle filling impairment rather than systolic dysfunction may in fact best characterize the earliest functional abnormality in preclinical alcoholic cardiomyopathy. Of the few comparable earlier data, those of Lundin et al⁵ and Silberbauer et al⁶ support our findings, whereas Dancy et al⁷ did not detect any difference in left ventricular filling by M-mode echocardiography between alcoholics and carefully matched controls. Doppler and M-mode filling indexes are not very closely related,¹⁶ however, because the former reflect global filling and the latter describe segmental ventricular function only. Of importance, the Doppler method has proved sensitive to both acute and chronic diastolic impairment and, given certain preconditions, it also helps to distinguish abnormal relaxation from reduced compliance.¹⁷⁻¹⁹

Diastolic dysfunction in asymptomatic alcoholics: relaxation or compliance abnormality? Diastole can be divided into an early energy-demanding period governed by myocardial relaxation and into a phase of passive filling, which also includes the booster effect of atrial contraction. Our data suggest that an impairment of relaxation and active filling is the predominant mechanism of diastolic dysfunction in preclinical alcoholic car-

diomyopathy. The pattern of changes in the Doppler indexes with reduced acceleration and peak velocity of the early flow, prolonged relaxation time and increased late-to-early peak velocity ratio is characteristic of a primary relaxation abnormality.¹⁷⁻¹⁹ In theory, low left atrial pressure could have caused similar changes but there was no indication of hypovolemia in our subjects and, if anything, alcoholics tend to have high instead of low filling pressures in the left side of the heart.^{1,4} Unlike us, Thomas et al⁸ concluded that a compliance impairment is the first functional manifestation of alcoholic heart muscle disease. Their study was made in dogs, however, and the assessment of compliance was based only on measuring the increases in left ventricular end-diastolic pressure and volume during saline infusion. Although this technique may detect alterations in overall diastolic function, it may not be able to distinguish incomplete relaxation from reduced compliance. It is worthy of emphasis that the changes in Doppler indexes in our alcoholic patients should have been just the opposite had a reduction in compliance constituted the leading diastolic abnormality.¹⁷⁻¹⁹

Studies of animals have shown that chronic alcohol use impairs the uptake of calcium ions from the sarcoplasm into the sarcoplasmic reticulum.^{20,21} This kind of defect inevitably delays the inactivation of the actomyosin interaction and therefore has the potential to reduce the rate of myocardial relaxation. Our findings have thus a logical explanation in the altered biochemistry of the alcoholic heart muscle. Furthermore, the increased wall thickness may diminish the loading of the ventricle during late systole and early diastole, which also slows the relaxation.²² Although low-grade asynchrony of left ventricular function may in theory also have contributed to the filling impairment in our alcoholics,²² we have no positive evidence thereof.

Alcoholic heart muscle abnormalities in relation to the duration and quantity of heavy drinking: Although diastolic left ventricular function was clearly different in alcoholics and healthy subjects, there was no relation within the former group between the Doppler indexes and either the duration of alcoholism or the quantity of the most recent uninterrupted alcohol exposure. Unreliable reporting of drinking history could readily explain this finding, but it is worthy of recognition that alcoholism was a known and "accepted" vice in our study and the alcoholics therefore had little reason to keep their true drinking habits from the examiner. On the presumption that we are dealing with a true phenomenon, our data are compatible with a nonlinear relation between diastolic function and the quantity of cumulative alcohol exposure. There could exist a threshold of consumption—exceeded by all of our alcoholics—above which there was little further progression of diastolic abnormalities among asymptomatic patients. In agreement with this, Thomas et al⁸ detected diastolic dysfunction after 18 months of daily ethanol exposure in dogs, but no progression over the next 34 months of identically heavy drinking. The limitations of the Doppler method to identify different degrees of heart muscle injury must also be considered. It has recently been

shown that once the left atrial pressure begins to increase, a "pseudonormalization" of altered Doppler indexes may occur.^{18,19} As a corollary, myocardial disease of greater severity may be associated with less abnormal Doppler indexes if it has advanced into the stage of congestive heart failure. This fact undoubtedly decreases the usefulness of the Doppler indexes in such regression analyses as performed in our study. However, none of our alcoholics had either symptoms or radiologic signs of pulmonary venous congestion.

There exist very little earlier data about the relation of left ventricular diastolic or systolic function to either or both the reported duration and quantity of drinking among alcoholics. In the study by Silberbauer et al,⁶ no association was found between left ventricular diastolic function and the duration or magnitude of chronic alcoholism. Likewise, Askanas et al²³ reported that the mass and systolic function of the left ventricle were independent of the duration of excessive drinking. In fact, only Urbano-Marquez et al²⁴ have been able to detect a statistically significant relation between self-reported alcohol consumption and cardiac abnormalities among alcoholics. In their study, both the mass and ejection fraction of the left ventricle correlated with the estimated total lifetime dose of alcohol ($r = 0.45$ and -0.46 , respectively), but no comparable data on diastolic function were reported.

In conclusion, our study suggests that abnormal left ventricular filling is common in asymptomatic alcoholics and that it results predominantly from impaired relaxation. Diastolic function of the left ventricle may be more sensitive to the cardiotoxicity of ethanol than its systolic performance.

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Physiologic Peripheral Pulmonic Stenosis in Infancy

Ricardo J. Rodriguez, MD, and Thomas W. Riggs, MD

We studied 14 premature infants with the clinical diagnosis of peripheral pulmonic stenosis (PPS) and 15 normal full-term neonates by echocardiographic Doppler examinations. The PPS group had an average main pulmonary artery (PA) diameter similar to the control group (0.91 vs 0.96 cm, difference not significant), but had smaller branch PA diameters: right PA = 0.41 vs 0.50 cm, $p < 0.001$, and left PA = 0.41 vs 0.49 cm, $p < 0.001$. The PPS group also had greater peak velocities in the main PA (76 vs 63 cm/s, $p < 0.05$), right PA (193 vs 118 cm/s, $p < 0.001$) and left PA (187 vs 123 cm/s, $p < 0.001$). Similarly, the ratio of peak velocity in the branch/main PA was greater for the PPS group: right/main PA peak velocity = 2.91 vs 1.92, $p < 0.01$, and left/main PA peak velocity = 2.73 vs 1.99, $p < 0.05$. The calculated right ventricular output for the PPS group was more than the control group: 437 vs 261 ml/min/kg, $p < 0.001$. Hematocrits were not done on the control group, but the PPS group had an average hematocrit which was low (34%). It is concluded that patients with PPS have mild underdevelopment of the PA branches, with consequent increased flow velocity and turbulent flow. This turbulent flow may be contributed to by increased cardiac output and mild anemia.

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Transient peripheral pulmonic stenosis (PPS) is very common in infants and its incidence has been reported to be 67% in premature infants and 5% in full-term neonates.¹ This variety of functional murmur is distinctive in that the murmur radiates widely from the precordium to the axillas and the back and typically disappears by 3 to 6 months of age. Although the clinical course is benign, the murmur may be loud enough to raise the suspicion of congenital heart disease. Although this is a common precordial murmur of infancy, there is little reported information on this topic. We used echocardiography to examine 14 patients with PPS and compared them with 15 normal controls. This report compares and contrasts the findings in normal infants with those of the patients with PPS.

METHODS

Patients: The patient group consisted of 14 infants with the clinical diagnosis of PPS. Each patient had a grade 2 or 3 systolic ejection murmur over the mid- and upper left sternal border which radiated widely over the chest. Most of the patients were former premature infants (mean gestational age 28 ± 3 weeks) who were examined at a mean postnatal age of 33 days. All patients had a complete echocardiographic examination that demonstrated normal cardiac structures, although each of the patients had a patent foramen ovale. Hematocrits were available from 13 of 14 PPS patients at or within days of their echocardiographic examination.

The normal control group consisted of 15 full-term neonates who were free of congenital heart disease. The patients were all older than 48 hours at the time of their examination; none had a patent ductus arteriosus and each had a patent foramen ovale. Each had normal results on clinical cardiac examination. All of the control group patients were studied after written parental consent; the study had the approval of the hospital human investigation committee.

Echocardiographic examination: Complete 2-dimensional, Doppler and color Doppler echocardiographic examinations were performed on each patient using a Hewlett-Packard ultrasonoscope with a 5.0-MHz transducer. The examinations were recorded using standard VHS format and thermal printing paper at a speed of 100 mm/s. Each patient underwent range-gated Doppler examination of the main pulmonary artery (PA) and its branches. From a standard parasternal short-axis view, the Doppler cursor was placed in the main PA at an angle as nearly parallel as possible to blood flow to record the maximal velocity in the vessel. The branch

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PAs were also examined by Doppler interrogation with the sample volume placed in the proximal right and left PAs. Frequently, an angle correction factor was necessary for the right PA, because the velocity was not parallel to the Doppler signal. No correction factor was usually needed for the left PA.

The diameters of the main and branch PAs were each measured directly from the VHS image with all measurements in end systole (at the end of the T wave of the electrocardiogram). With the aid of a computer-interfaced digitizer tablet the following parameters were measured: maximal peak velocities in the main, right and left PAs; velocity-time-integral (Doppler area) in the main, right and left PAs and the RR interval.

From these measurements the following ratios were computed: right/main PA peak velocity ratio, left/main PA peak velocity ratio, right/main PA area ratio, left/main PA area ratio and heart rates. We also estimated right ventricular cardiac output using the relation cardiac output = heart rate \times main PA Doppler area \times (main PA diameter) squared \times 0.7854.²

Data analysis: All values are reported as mean \pm 1 standard deviation and each patient's values were the average of 3 measurements. An unpaired *t* test was used for statistical analysis and *p* < 0.05 indicated a significant difference between groups.

RESULTS

Clinical profile (control group): The results are listed in Table I (Figure 1). The mean weight was 3.54 kg. The mean main PA diameter was 0.96 cm, whereas the right PA was 0.50 cm and the left PA was 0.49 cm. The mean ratio of right/main PA diameter was 0.53, whereas the mean left/main PA diameter ratio was 0.52. The mean peak velocities in the PA were: main = 63 cm/s, right = 118 cm/s and left = 123 cm/s. The average ratio of peak velocities was 1.92 for the right/main PA,

TABLE I Comparison of Normal Neonates and Patients with Peripheral Pulmonic Stenosis (PPS)

	Normals (n = 15)	PPS (n = 14)	p Value
Heart rate	121 (10)	154 (25)	<0.001
MPA diameter (cm)	0.96 (0.12)	0.91 (0.09)	NS
RPA diameter (cm)	0.50 (0.06)	0.41 (0.04)	<0.001
LPA diameter (cm)	0.49 (0.05)	0.41 (0.04)	<0.001
MPA peak velocity	63 (9.3)	76 (17)	<0.05
RPA peak velocity	118 (27)	193 (38)	<0.001
LPA peak velocity	123 (18)	187 (43)	<0.001
MPA Doppler area	10 (1)	12 (2)	<0.05
RPA Doppler area	18 (4)	30 (6)	<0.001
LPA Doppler area	18 (3)	28 (6)	<0.001
Cardiac output/kg	261 (67)	437 (150)	<0.001
RPA/MPA diameter	0.53 (0.06)	0.46 (0.04)	<0.005
LPA/MPA diameter	0.52 (0.09)	0.45 (0.03)	<0.01
RPA/MPA peak	1.92 (0.50)	2.91 (1.12)	<0.01
LPA/MPA peak	1.99 (0.37)	2.73 (1.24)	<0.05
Weight	3.54 (0.34)	2.74 (0.57)	<0.001
Hematocrit	NA	34.2 (6.9)	

Area = velocity time integral of doppler flow; cardiac output/kg = calculated stroke volume \times heart rate divided by weight in kg; LPA = left pulmonary artery; MPA = main pulmonary artery; NA = not available; peak = maximal velocity in cm/s; RPA = right pulmonary artery.

whereas the corresponding ratio was 1.99 for the left/main PA. The estimated mean right ventricular cardiac output was 261 ml/min/kg. Because these were asymptomatic full-term neonates, hematocrits were not obtained.

Clinical profile (peripheral pulmonic stenosis group): The results are listed in Table I (Figure 2). The mean weight was 2.74 kg. The mean main PA diameter was 0.91 cm, whereas the right PA was 0.41 cm and the left PA was 0.41 cm. The mean ratio of right/main PA diameter was 0.46, whereas the mean left/main PA di-

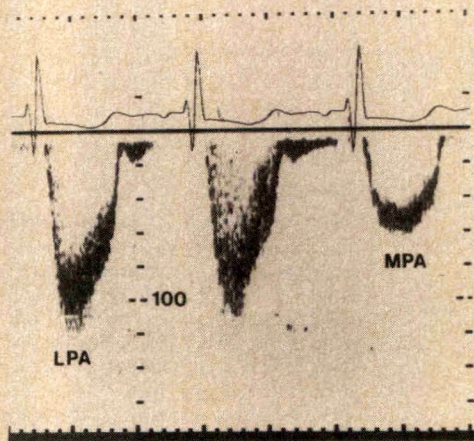


FIGURE 1. This Doppler echocardiogram represents a range-gated study of a normal neonate in whom the sample volume was moved from the left pulmonary artery (LPA) to the main pulmonary artery (MPA). The respective peak velocities were 120 and 80 cm/s. The recording was made at 100 mm/s, and 100 cm/s calibration is shown.

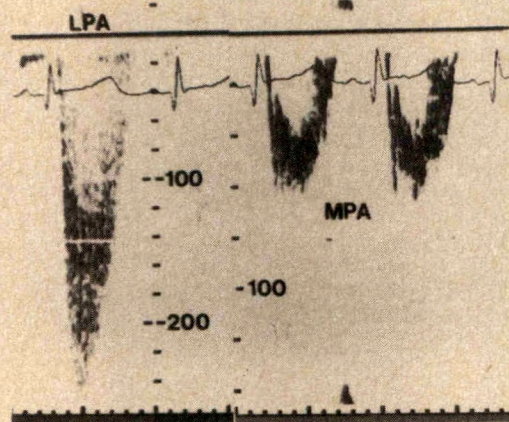


FIGURE 2. The Doppler echocardiogram represents a composite of 2 range-gated studies of an infant with peripheral pulmonic stenosis from the right pulmonary artery and the main pulmonary artery (MPA). The respective peak velocities were 245 and 62 cm/s. The recording was made at 100 mm/s, and 100 and 200 cm/s calibration is shown. (Note the different velocity scales.) LPA = left pulmonary artery.

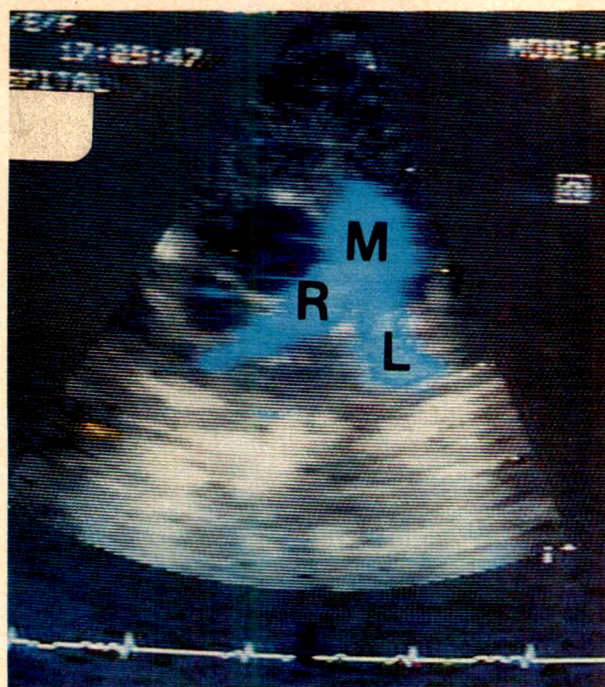


FIGURE 3. The 2-dimensional color echocardiogram was recorded from a normal neonate during late ventricular systole and displays a uniform flow velocity in both the main (M) and branch right and left (R and L) pulmonary arteries.

ameter ratio was 0.45. The mean peak velocities in the PA were: main = 76 cm/s, right = 193 cm/s and left = 187 cm/s. The average ratio of peak velocities was 2.91 for the right/main PA, whereas the corresponding ratio was 2.73 for the left/main PA. The estimated mean right ventricular cardiac output was 437 ml/kg/min. Hematocrits were available from 13 of 14 patients (mean 34%).

Comparison of control group with peripheral pulmonary stenosis group (Table I, Figures 3 and 4): The average weight for the control group was significantly greater for the PPS group (3.54 vs 2.74 kg, $p < 0.001$). However, the main PA diameters were not significantly different (0.96 vs 0.91 cm, $p = 0.21$). The mean diame-

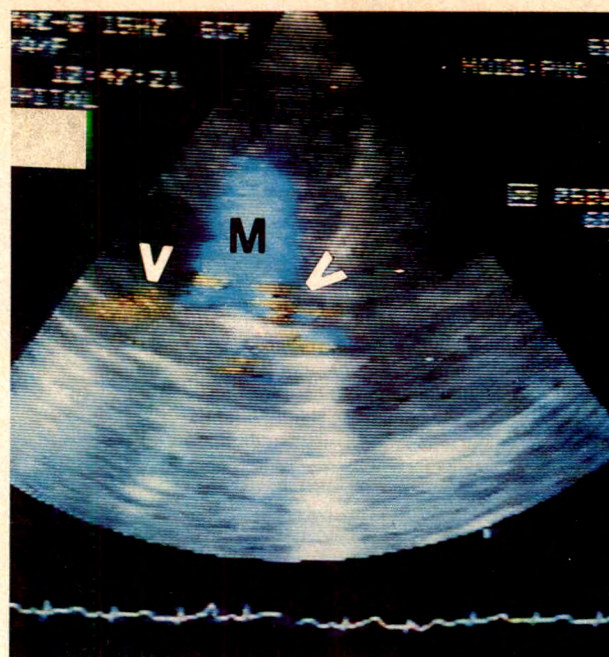


FIGURE 4. The 2-dimensional color echocardiogram was recorded from an infant with peripheral pulmonary stenosis during late ventricular systole and displays a low velocity uniform flow pattern in the main (M) pulmonary artery and aliasing in the branch right and left (R and L) pulmonary arteries. Note also the small caliber of the branch pulmonary arteries compared with the main pulmonary artery. (Arrowheads highlight the origin of the pulmonary artery branches.)

ters of both the right (0.50 vs 0.41 cm, $p < 0.001$) and the left (0.49 vs 0.41 cm, $p < 0.001$) PA were significantly less for the PPS group than for the control group. The peak velocities in the PA were significantly higher for the PPS group than for the control group, especially in the branch PA: main PA 63 vs 76 cm/s, $p < 0.05$; left PA 123 vs 187 cm/s, $p < 0.001$; and right PA 118 vs 193 cm/s, $p < 0.001$.

Expressed as ratios, the branch PA versus main PA diameters were slightly, but significantly, less for the PPS group than for the control group: left/main diameter ratio, 0.52 vs 0.46, $p < 0.01$; and right/main diame-

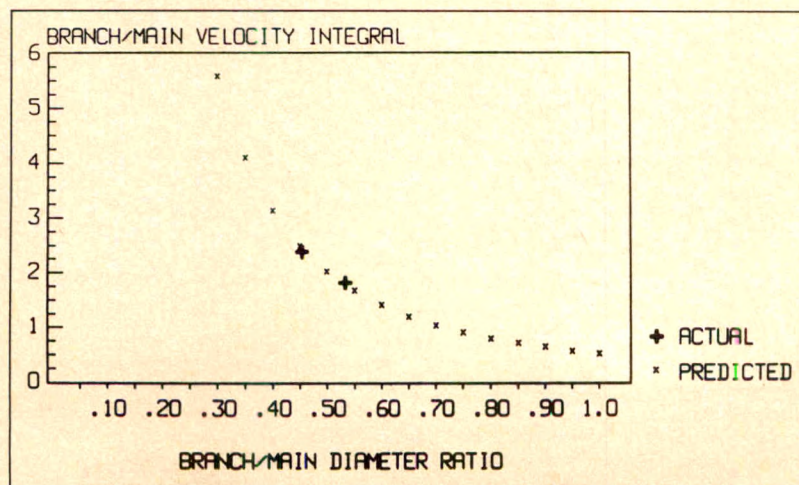


FIGURE 5. Relation between the branch/main pulmonary artery diameter (expressed as a ratio) and the ratio of branch/main pulmonary artery peak velocities. The predicted values assume: (1) equal pulmonary artery branch diameters, and (2) equal distribution of flow into each branch pulmonary artery. This model is nonlinear and predicts a large increase in branch pulmonary artery peak velocity when the branch pulmonary artery diameter is reduced <50% of the main pulmonary artery diameter. "Actual" values represent the mean values for the normal neonates and the patients with peripheral pulmonary stenosis, respectively.

ter ratio, 0.52 vs 0.45, $p < 0.05$. The ratio of peak velocities in the branch versus the main PA was also significantly higher for the PPS group than for the control group: left/main peak velocity ratio, 1.99 vs 2.73, $p < 0.05$; and right/main peak velocity ratio, 1.92 vs 2.91, $p < 0.01$. The estimated right ventricular cardiac outputs were significantly higher for the PPS group than for the control group (437 vs 261 ml/kg/min).

DISCUSSION

Transient PPS is a common precordial murmur of infancy and it is particularly frequent in premature infants. In the fetus, most of the right ventricular output passes through the patent ductus arteriosus to the descending aorta and only about 10% of the combined ventricular output passes into the branch PAs.³ We suggest that this murmur results from turbulent flow at the point of sudden tapering of the branch PAs compared with the main PA and coincident increased velocity in the branch PAs. Perhaps contributing to this turbulent flow is the frequent mild "physiologic anemia" of the premature infant. To a lesser extent, the same phenomenon is observed in full-term normal neonates, but the tapering is less abrupt, the increase in PA velocity is less marked, the hemoglobin concentration is greater and the flow remains nonturbulent.

Cardiac catheterization data from neonates with PPS demonstrate a pressure gradient from the main to the branch PAs, consistent with obstruction at the origin of the branch PAs.⁴ This pressure gradient may have been accentuated in the PPS group because of their lower hematocrits, higher right ventricular output and decreased pulmonary vascular resistance compared with those of the full-term control group. Although we excluded congenital heart disease (and a patent ductus arteriosus) by echocardiography in our PPS patients and in the control group, we cannot exclude the contribution of a left-to-right shunt through a patent foramen ovale to increased pulmonary blood flow. However, a patent foramen ovale was universal in both the PPS and control groups and no patient had findings of right atrial or right ventricular volume overload.

The concept of the Reynold's number, which is a ratio of inertial to viscous forces, is useful in characterizing flow in arteries.⁵ This number is calculated as $Re = V \cdot D \cdot \rho / (\eta)$, where V = average velocity/cross-sectional area, D = diameter, ρ = density and η = viscosity. When the PPS group was compared with the normal controls, the former had a greater flow velocity and presumably a lower viscosity; thus, we speculate that the Reynold's number would be higher, implying turbulent flow.^{6,7}

We also speculate (Figure 5) on the relation between the branch/main PA diameter and the ratio of branch/main PA velocity time integrals ("Doppler area" in Ta-

ble I). Assuming that the PA branch diameters are equal and that there is equal distribution of flow into each branch, the continuity equation (conservation of mass) states that the product of the velocity time integral and the cross-sectional area of the main PA must equal the sum of the respective products in the branch PAs.⁵ This model is nonlinear and predicts a large increase in branch PA peak velocity when the branch PA diameter is reduced $< 50\%$ of the main PA diameter.

Our control group of normal neonates was full-term, since premature infants at the postnatal age and weight of the PPS patients very frequently had a PPS murmur. In fact, it was difficult to find a group of premature infants of this postnatal age and weight who did not have a murmur of PPS.

The PPS study group and the normal controls were different in several respects. Although the main PA diameters were essentially the same for the 2 groups, the branch PA diameters and the ratio of branch/main PA diameters were each significantly less for the PPS group, implying underdevelopment of the PA branches. The smaller PA branch development resulted in higher peak velocities in the branch PAs and a greater ratio of branch/main PA peak velocity. We hypothesize that this greater velocity results in turbulent flow, generating the characteristic murmur of PPS.

Aliasing of the color Doppler image of the PA branches may be confused with retrograde flow seen in the PA of an infant with a patent ductus arteriosus (Figure 4). The PPS color Doppler findings can be differentiated from those of a patent ductus arteriosus by the timing and the location of the aliased signal. The PPS patients would show an aliased signal during systole at the point of branching of the PAs, whereas the patient with a left-to-right shunt through a patent ductus arteriosus would demonstrate continuous retrograde flow from the patent ductus arteriosus into the main PA.

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Coronary Arteries in Truncus Arteriosus

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Nicholas Noriega-Ramos, MD, and Stanislaw Sadowinski, MD

The origin and distribution of the coronary arteries was described in 39 autopsy specimens of truncus arteriosus (TA). The specimens were classified according to the number and the patterns of the truncal cusps. The position of the truncal cusps was defined in relation to intracardiac structures, namely, the atrioventricular orifices. Bicuspid truncal valves were observed in 8 cases (21%), tricuspid in 22 cases (56%) and quadricuspid in 9 cases (23%). All tricuspid valves had 2 anterior and 1 posterior cusp. Great variability in the origin of the coronary arteries was observed, with a tendency for the right coronary artery to arise from the anterior right quadrant and for the left coronary artery to arise from the anterior and left quadrant. Such a tendency was observed in 50% of the bicuspid, in 59% of the tricuspid and in 66% of the quadricuspid valves. The anatomic right ventricle was always observed to be vascularized by a right coronary artery, and the anatomic left ventricle by a left coronary artery, even in cases in which there was a single coronary trunk. The anterior surface of the right ventricle was crossed by a right coronary artery in 5 cases. A single coronary artery was observed in 7 cases (18%). Embryologic considerations are offered, especially regarding the relation between the observed variability in coronary artery patterns in TA and the absence of the truncal septation.

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Truncus arteriosus (TA) is a congenital cardiovascular malformation in which a single arterial trunk arises from the base of the heart by way of a single semilunar (truncal) valve.¹⁻³ This trunk gives origin to the coronary arteries and supplies directly the systemic and pulmonary circulations.^{1,2,4,5} Beneath the truncal valve, there is a ventricular septal defect that leads to the existence of a single fibromuscular outlet (common outlet).

Reports on TA are extensive and refer to some aspects of the coronary anatomy,^{1,3-8} but only 2 systematically studied the coronary arteries in relation to their origin and distribution.^{6,9} A relevant discussion that remains open in the embryogenesis of the coronary arteries is the relation between coronary ostia and truncal septation.¹⁰ Current surgical techniques for the correction of TA require not only the knowledge of the origin of the coronary arteries, but also of their topographic distribution.⁶ The present report uses these 2 parameters to describe the patterns of the coronary arterial circulation in this congenital heart defect.

METHODS

We studied the coronary arteries in 39 autopsy specimens with TA: 28 belonged to the Service of Pathologic Anatomy of the Hospital de Cardiologia of the National Medical Center of the Mexican Institute of Social Security, and 11 to the Service of Pathologic Anatomy of the Hospital Infantil de Mexico "Federico Gomez."

We classified the truncal cusps by using 2 parameters, the number and the spatial position. We subdivided the specimen according to the number of cusps (bicuspid, tricuspid and quadricuspid). We defined the position of each cusp in relation to the atrioventricular orifices in the coronal plane. We called cusps adjacent to these orifices, posterior, and those not contiguous to these orifices, anterior. The axis in the coronal plane, orthogonal to the line that joins the geometric centers of each atrioventricular valve, was called anteroposterior. Looking at the frontal aspect, we called right and left what is to the right or left of the anteroposterior axis. Right-left and anteroposterior classifications are not then necessarily identical to the reference axis of the whole body, according to these definitions.

The coronary arteries were dissected and a detailed description of the origin and course of the trunks and main coronary branches obtained. We identified the right and left coronary arteries according to their areas of vascularization.¹⁰ The vascularization area of the right coronary artery is the anatomic right ventricle,

and the area of the left coronary artery is the anatomic left ventricle.

RESULTS

All 39 specimens featured situs solitus of the atria and atrioventricular concordance. The coronary findings were described according to the 3 main truncal valve patterns: bicuspid, tricuspid and quadricuspid.

BICUSPID TRUNCAL VALVES: These were 8 cases (21% of 39). The position of the cusps were found to be either in a right-left or in an anteroposterior pattern (Figure 1).

A right and a left cusp: There were 5 cases (63%). Both cusps were adjacent to the atrioventricular orifices (Figure 1, A and B). In 4 cases the right coronary artery arose from the right cusp, in proximity to the anterior commissure, and the left coronary artery arose from the middle portion of the left cusp (Figure 1A). In another case, the right coronary artery arose on top of the posterior commissure and the left coronary artery arose in the midsegment of the left cusp (Figure 1B).

One anterior and one posterior cusp: There were 3 cases (38%). In 1 case, the left coronary artery arose from the middle portion of the posterior cusp and the right coronary artery originated in the middle portion of the anterior cusp (Figure 1C). In another case, both coronary arteries arose juxtaposed against the middle portion of the posterior cusp (Figure 1D). In the last case, a single coronary trunk arose from the posterior cusp and then split into right and left coronary arteries (Figure 1E).

TRICUSPID TRUNCAL VALVE: There were 22 cases (56% of 39). All of these featured a posterior cusp, adjacent to the atrioventricular orifices, and 2 anterior cusps, the right and the left (Figure 2). In 13 of these cases (59%), the right coronary artery arose from the anterior and right cusp, close to the anterior commissure, whereas the left coronary originated from the anterior left cusp, in proximity of the anterior commissure, and then subdivided normally (Figure 2A). Less frequent patterns are illustrated in Figures 2B to 2H.

QUADRICUSPID TRUNCAL VALVE: There were 9 cases (23% of 39). Two coronary cusp patterns were observed:

the posterior, anterior, right and left, and the 2 posterior (right and left) and 2 anterior (right-left), as shown in Figure 3.

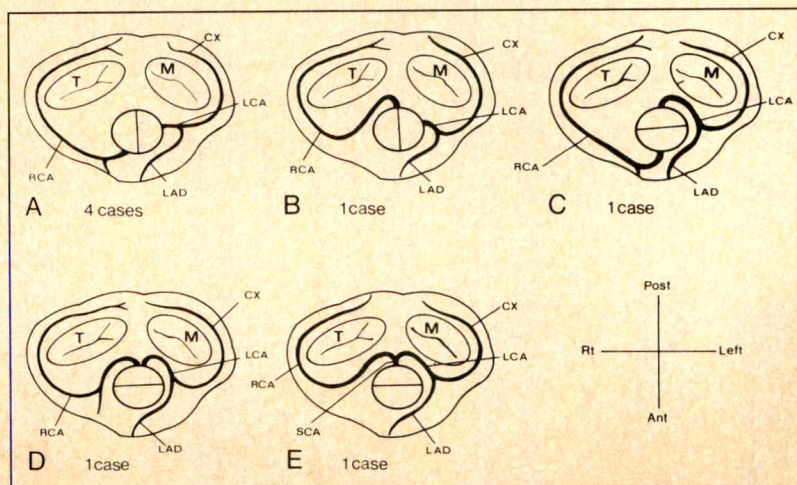
Posteroanterior right and left cusps: There were 8 cases (89% of 9). In 6, the right coronary artery arose from the right cusp, close to the anterior right commissure, and the left coronary arose from the midportion of the left cusp and then subdivided normally (Figure 3A). In 1 case, a single coronary trunk arose from the midportion of the posterior cusp and then subdivided into a right coronary artery and into a left coronary artery (Figure 3B). In another case, a single coronary trunk arose from the midportion of the anterior cusp and then subdivided into 3 branches: anterior descending, right coronary, which crossed the upper anterior surface of the right ventricle, and circumflex arteries (Figure 3C).

Two posterior right and left, and two anterior right and left cusps: There was 1 case (11% of 9). The right coronary artery arose from the midportion of the anterior right cusp, and the left coronary artery arose from the midportion of the posterior left cusp and then subdivided into the circumflex and anterior descending branches (Figure 3D).

DISCUSSION

Anatomic findings: The incidence of bi-, tri- and quadricuspid valves was 21, 56 and 23%, respectively, in our series of 39 autopsy specimens of TA. This finding is similar to those previously reported.¹⁻⁹ Unfortunately, our anatomic description of the truncal cusps cannot be reliably compared with any published report, because previous investigators addressed the subject without strict anatomic references. We believe that, in the study of complex congenital heart diseases, intracardiac structures cannot be consistently described in reference to the axis of the whole body. Because of the possibility of anomalies in the position of the apex inside the thorax (dextroversions, mesocardias, crisscrossed hearts, and so forth), cardiac descriptions should make reference to the main intracardiac structures. We elected to define the truncal cusps in terms of their relations to the atrioventricular orifices, as explained. It is important to recognize that this methodologic adjustment has resulted

FIGURE 1. Diagrammatic representation of the origin and distribution of the coronary arteries in truncus arteriosus with bicuspid valve. A, B, right and left cusps; C, D, E, anterior and posterior cusps. ANT = anterior; CX = circumflex; LAD = left anterior descending artery; LCA = left coronary artery; M = mitral; POST = posterior; RCA = right coronary artery; RT = right; SCA = single coronary artery; T = tricuspid.



in the recognition of different cusp patterns within each class (bi-, tri-, quadricuspid) heretofore overlooked in previous reports. We observed 5 different patterns of the truncal cusps in TA and could not recognize a predominant coronary origin in these cardiac defects, as expected in normal hearts. In our series of 39 cases, we found 17 different coronary patterns (Figures 1, 2 and 3, A and B), with an increased incidence of a single coronary artery (18%), as compared with normal hearts. Such variability in the anatomy of the proximal coronary trunks contrasts with the essentially consistent

peripheral coronary branching pattern (the right, the left anterior descending and circumflex arteries). Figure 4 shows the sites of the coronary ostia (right, left and single) observed in our series, in reference to the circumference of the truncal valve, independent from the truncal cusps configuration. The widespread distribution of the coronary ostia recognized only a tendency for the left coronary artery to arise from the anterior and left section of the truncal anulus, whereas the right coronary artery generally originates from the anterior and right section. Still, a significant percentage of the ori-

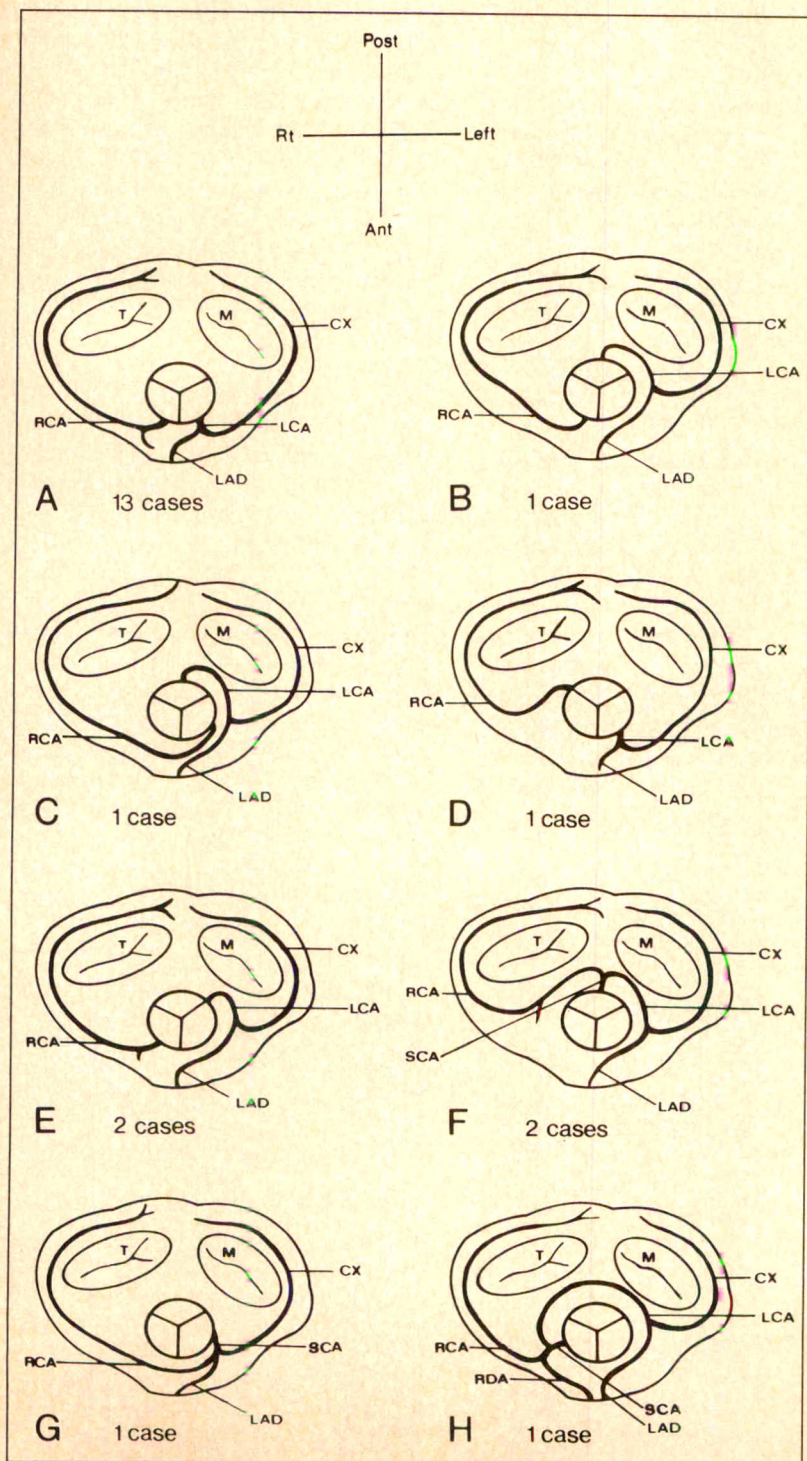


FIGURE 2. Diagrammatic representation of the origin and distribution of the coronary arteries in truncus arteriosus with tricuspid valve, with 2 anterior and 1 posterior cusp. Abbreviations as in Figure 1.

fixes (11 of 60, 18%) are situated in the posterior quadrant of the truncal anulus, a definite difference from the usual patterns in a normal aorta. This finding could be interpreted as a demonstration of the absence of an equivalent to what in the normal heart is the "noncoronary" cusp in hearts with TA.¹⁰

In cases of a single coronary artery, its origin can be quite variable, with a tendency to originate from the

posterior quadrant (Figure 4). A single coronary artery was found at a similar incidence (4 to 18%) by various investigators, as shown in Table I. Similar variability of coronary origination has been reported.^{1,3,5-7,9}

The course of the main coronary arteries in TA seems to follow the atrioventricular and interventricular grooves,^{6,9} as in the normal heart with a single exception: the anterior upper surface of the right ventricle

FIGURE 3. Diagrammatic representation of the origin and distribution of the coronary arteries in truncus arteriosus with quadricuspid valve. *A, B, C*, posteroanterior right and left cusps. *D*, 2 posterior and 2 anterior cusps (right and left). Abbreviations as in Figure 1.

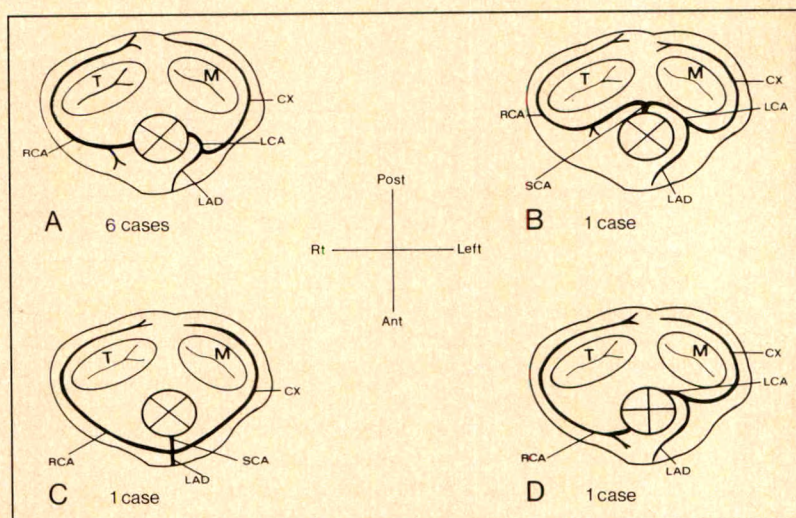


FIGURE 4. Diagrammatic representation of the origin of the coronary arteries in our series of 39 cases. The truncal wall is subdivided into 4 conventional quadrants. Abbreviations as in Figure 1.

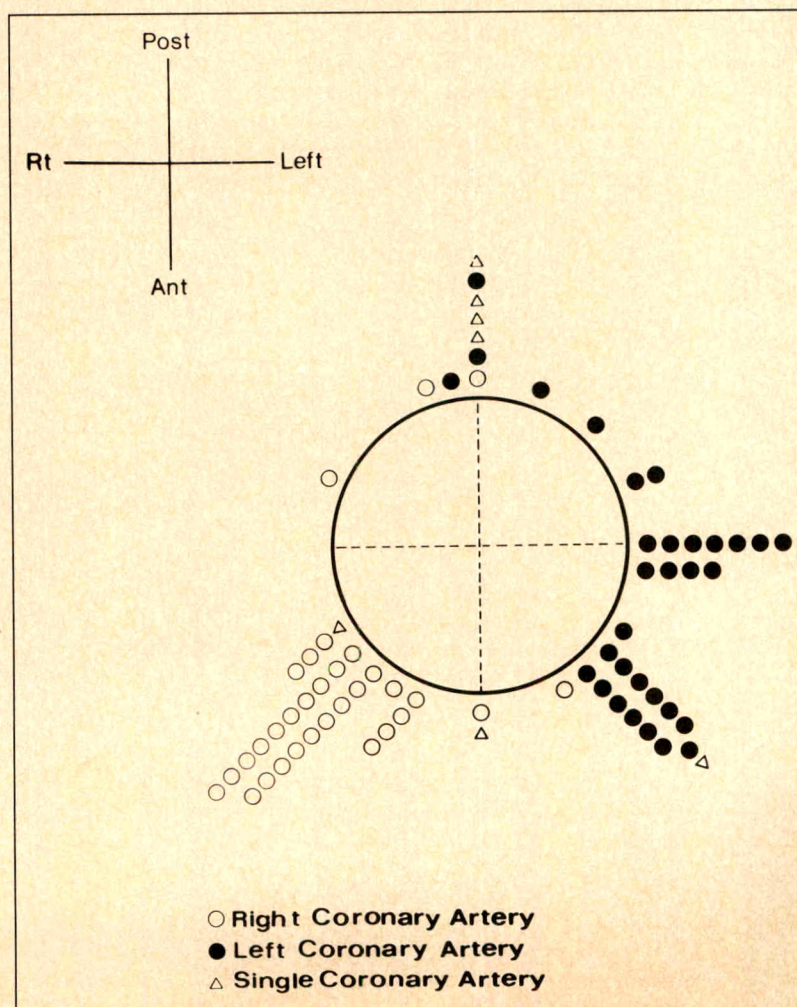


TABLE I Single Coronary Artery in Truncus Arteriosus

Investigators	Year of Publication	Autopsy Specimens (no.)	Single Coronary Arteries (no., %)
Bharati et al ⁷	1974	180	11 (6)
Calder et al ⁵	1976	100	4 (4)
Shrivastava and Edwards ⁹	1977	30	4 (13)
Crupi et al ¹	1977	66	8 (12)
Anderson et al ⁶	1986	31	4 (13)
Butto et al ³	1986	53	10 (19)
De la Cruz MV*	1990	39	7 (18)

* Results of present study.

was found to be crossed by a major coronary artery in 5 of our 39 cases (13%). This is of special relevance to the surgical repair of TA, which involves an anterior right ventriculotomy (Figures 1C, 2C, 2G, 2H and 3C). Selective coronary angiography may play an important part in the preoperative evaluation of these cases. In no instance did we find an intramyocardial course of a major coronary artery or branch.

From a morphogenetic viewpoint, the major interest of our observations relates to the consequences of the absence of an aortopulmonary septum, in the determination of the coronary arterial patterns.¹¹⁻¹⁴ The distal coronary anatomy does not seem to be altered in this, as in other defects of the truncoconal septation.¹² The left anterior descending, circumflex and right coronary arteries follow normal pathways and patterns, whereas the proximal coronary anatomy is profoundly upset in TA, with an observed wide spectrum of coronary ostia locations and quite an increased incidence of a single

coronary artery. The coronary ostia are consistently located at the truncal sinuses, whereas the absence of aortopulmonary septation would seem to result in a substantial disturbance in the determination of coronary ostial number and location.

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Spectrum of Hemodynamic Changes in Cardiac Tamponade

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To investigate the pathophysiology of cardiac tamponade, the hemodynamics of 77 consecutive patients with >150 ml of pericardial effusion were studied. Patients were classified into 3 groups based on the equilibration of intrapericardial with right atrial and pulmonary arterial wedge pressures (mm Hg): group I (n = 16), intrapericardial pressure was less than right atrial and pulmonary arterial wedge pressures; group II (n = 13), intrapericardial pressure was equilibrated with right atrial but not pulmonary arterial wedge pressures; group III (n = 48), intrapericardial pressure was equilibrated with right atrial and pulmonary arterial wedge pressures. Pericardiocentesis produced the following changes: group I—significant ($p < 0.03$) decreases in intrapericardial pressure (7 ± 2 mm Hg), right atrial pressure (3 ± 2 mm Hg), pulmonary arterial wedge pressure (2 ± 2 mm Hg), and the inspiratory decrease in arterial systolic pressure (3 ± 4 mm Hg) but no significant change in cardiac output; group II—significant ($p < 0.02$) decreases in intrapericardial pressure (11 ± 5 mm Hg), right atrial pressure (6 ± 4 mm Hg), pulmonary arterial wedge pressure (4 ± 5 mm Hg), and inspiratory decrease in arterial systolic pressure (8 ± 7 mm Hg), and increase in cardiac output (1.1 ± 1.2 liters/min); group III—significant ($p < 0.001$) decreases in intrapericardial pressure (16 ± 7 mm Hg), right atrial pressure (9 ± 4 mm Hg), pulmonary arterial wedge pressure (8 ± 5 mm Hg), inspiratory decrease in arterial systolic pressure (17 ± 11 mm Hg), and increase in cardiac output (2.8 ± 1.5 liters/min). The changes after pericardiocentesis in all parameters were significantly ($p < 0.05$) greater in group III than in groups I or II except for the change in right atrial pressure, which was not significantly different in groups II versus III. The changes after pericardiocentesis indicate pericardial effusion caused the greatest abnormalities in group III but also caused significant abnormalities of pressure and flow in group II and of pressure alone in group I. Because hemodynamic alterations were noted in all groups, increasing in severity

from groups I to III, it is concluded that cardiac tamponade is not an "all-or-none" phenomenon, and the severity of hemodynamic derangement rather than its presence or absence should be assessed in patients with pericardial effusion.

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Based on hemodynamic observations in 18 patients with pericardial effusion, we had suggested that cardiac tamponade is an "all or none" phenomenon.¹ Our hypothesis was formulated as follows (Figure 1, left): With increasing fluid accumulation in the pericardial space, pericardial pressure increases progressively to equilibrate with right ventricular filling pressure. Up to this point, there are no changes in cardiac pressures or output (phase I). As further amounts of fluid enter the space, pericardial and right ventricular filling pressures increase together to equilibrate eventually with left ventricular filling pressure, which in most patients is greater than right ventricular filling pressure. Between these 2 ventricular filling pressure equilibration points, the pericardial effusion produces an elevation of right ventricular filling pressure and depression of cardiac output but no pulsus paradoxus. This phase was described as right heart tamponade (phase II). As more fluid accumulates, the 3 equilibrated pressures increase further, the magnitude of cardiac output depression increases and pulsus paradoxus appears (phase III). Experience with a larger group of patients, particularly with minimal hemodynamic changes, has taught us that the hemodynamic changes occur at the onset of pericardial effusion and worsen progressively as accumulation increases. In light of these new observations, the original concept has been revised and the supportive data are presented in this report.

METHODS

The patient population represents a consecutive series of patients undergoing diagnostic or therapeutic pericardiocentesis, or both, at Presbyterian-University Hospital from 1973 to 1987. Inclusion in this series required the patient to have had ≥ 150 ml of pericardial fluid aspirated and a complete hemodynamic study both before and after pericardiocentesis. A complete hemodynamic study was defined as measurement of right atrial, pulmonary arterial wedge and intrapericardial pressures and cardiac output. Right atrial and pulmonary arterial wedge pressures were recorded sequentially.

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Of 101 consecutive procedures with complete hemodynamic studies, 24 were excluded for the following reasons: effusive-constrictive pericarditis in 2, incomplete aspiration of fluid in 4, instability during catheterization as a result of volume replacement or loss in 4, effusion volume of <150 ml in 5, inability to recover the original hemodynamic data in 5 and technical problems in 4. One patient underwent 2 procedures. The data reported therefore consists of 77 procedures in 76 patients. The 76 patients consisted of 39 men and 37 women (average age mean \pm standard deviation 49 ± 17 years). The etiology of pericardial effusion was neoplastic in 23, uremic in 19, unknown in 13, postoperative in 8, infectious in 4, excessive anticoagulation in 3, connective tissues disease in 3, Dressler's syndrome in 2, and radiation in 1. Sinus rhythm was present in 73 patients and atrial dysrhythmias with irregular ventricular cycle lengths in 3 patients. Pressure measurements, pericardiocentesis and the determination of the inspiratory decrease in systolic pressure were performed as previously described.¹ Cardiac output determinations were performed in triplicate by the thermodilution method in 58 patients and in duplicate using indocyanine green as the indicator in the remaining patients. Intraarterial pressure recordings were obtained in 69 of the 74 patients in sinus rhythm. Pulsus paradoxus was defined as an inspiratory decline of arterial systolic pressure >12 mm Hg during a regular rhythm.² Percentage pulsus paradoxus was defined as >9% inspiratory decline of expiratory arterial systolic pressure.^{1,2} Equilibration of mean right atrial and intrapericardial pressure was defined as a difference ≤ 1 mm Hg; equilibration of mean right atrial and pulmonary arterial wedge pressures was defined as a difference ≤ 2 mm Hg. The percentage change in cardiac output after pericardiocentesis was calculated as (cardiac output after pericardiocentesis—before/before) $\times 100$. Based on repeated determinations of baseline cardiac outputs in our laboratory, a significant increase in output was considered to be $\geq 20\%$.² Patients were divided into 3 groups based on hemodynamic find-

ings before pericardiocentesis: group I = lack of equilibration between right atrial and pericardial pressures; group II = equilibration of right atrial and pericardial pressures but not pulmonary arterial wedge pressure; group III = equilibration of all 3 pressures.

Intragroup differences were assessed by Student's *t* test using paired data. One-way analysis of variance was used to determine the presence of mean differences among the 3 groups; if present, the differences between individual means was assessed by Scheffe's procedure at a significance level of 0.05.

RESULTS

There were 16 patients who met the hemodynamic criteria for group I (i.e., right atrial pressure was higher than pericardial pressure by ≥ 2 mm Hg [Table I, Figure 2]). In this group, the pericardial aspirate volume ranged from 270 to 1,860 ml (median value 408). Before pericardiocentesis, mean right atrial pressure exceeded pericardial pressure by an average of 3 ± 2 mm Hg and was less than pulmonary arterial wedge pressure by 4 ± 3 mm Hg. After aspiration, mean right atrial pressure decreased significantly from 10 ± 6 to 7 ± 6 mm Hg, and mean pulmonary arterial wedge pressure decreased significantly from 13 ± 7 to 12 ± 7 mm Hg. There was a slight but nonsignificant increase in cardiac output, from 5.8 to 6.0 liters/min. The inspiratory decline in arterial systolic pressure could be evaluated in 13 patients. The average decline decreased significantly from 12 ± 6 to 9 ± 6 mm Hg after the procedure. Pulsus paradoxus was present in 4 patients. It was abolished by pericardiocentesis in 2 patients (15 to 7 and 17 to 5 mm Hg) and persisted in the other 2 (28 to 22 and 19 to 19 mm Hg). Percentage pulsus paradoxus was present in 2 (10%, 22%) and persisted in 1 (16%) after the tap. In the 13 patients in group II (Table I), the pericardial aspirate volume ranged from 200 to 1,400 ml (median value 750). By definition, right atrial and pericardial pressures were equilibrated; pulmonary arterial wedge pressure was higher by 5 ± 2 mm Hg.

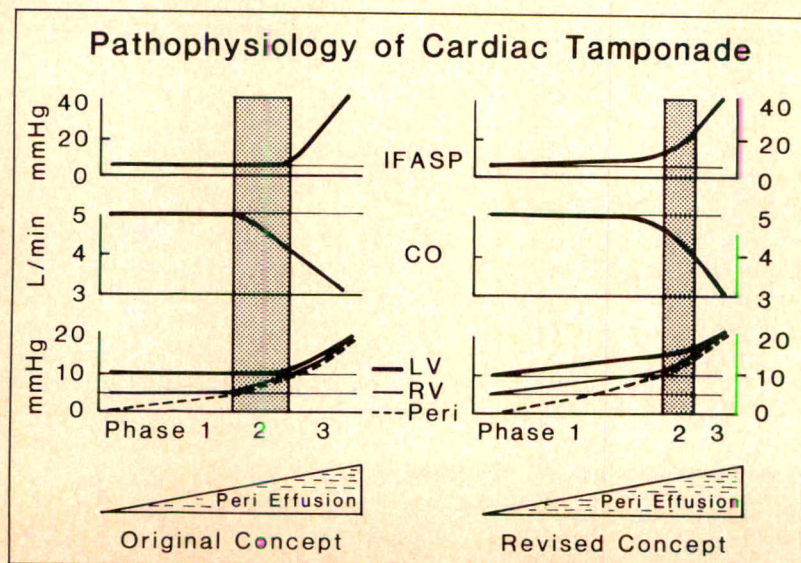


FIGURE 1. Schematic representation of hemodynamic changes including pericardial (Peri), right ventricular (RV), left ventricular (LV) and inspiratory decrease in arterial systolic pressures (IFASP) and cardiac output (CO), with increasing pericardial effusion in any given patient depicted by the increasing height of the triangle from left to right. Stippled vertical area indicates phase II. Left panel represents the original concept, and right panel represents the revised concept (see text for explanation).

TABLE I Hemodynamic Changes Associated with Pericardiocentesis

	No. of Pts.		RAP (mm Hg)			PAWP (mm Hg)			IPP (mm Hg)			CO (liters/min)			IFASP (mm Hg)		
			Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff
Group I	16	Mean	10	7	3	13	12	2	6	0	7	5.8	6.0	0.3	12	9	3*
		±SD	5	6	2	7	7	2	0.4	3	2	1.8	1.8	0.6	9	6	4
		p	<0.001			0.025			<0.001			0.113			0.010		
Group II	13	Mean	10	3	6	15	11	4	9	-2	11	5.2	6.3	1.1	16	8	8
		±SD	5	5	4	4	8	5	5	2	5	1.5	2.0	1.2	8	4	7
		p	<0.001			0.013			<0.001			0.005			0.004		
Group III	48	Mean	16	7	9	17	9	8	16	0	16	4.4	7.2	2.8	26	9	17†
		±SD	7	5	4	6	5	5	7	3	7	2.0	2.3	1.5	13	5	11
		p	<0.001			<0.001			<0.001			<0.001			<0.001		

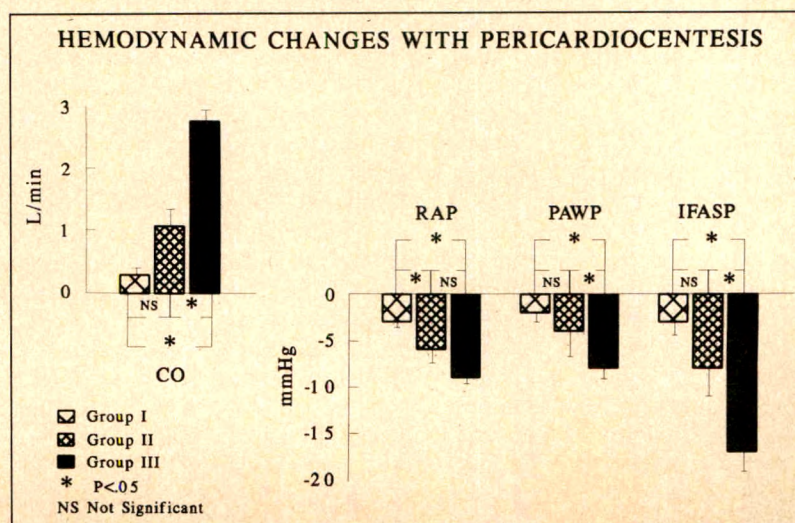
* n = 13; n = 11; † n = 45.

CO = cardiac output; Diff = difference; IFASP = inspiratory decrease in arterial systolic pressure between pre- and postreading; IPP = mean intrapericardial pressure; PAWP = mean pulmonary arterial wedge pressure; Post = after pericardiocentesis; Pre = before pericardiocentesis; RAP = mean right atrial pressure; SD = standard deviation.

Pericardiocentesis resulted in significant decreases in right atrial pressure (10 ± 5 to 3 ± 3 mm Hg) and left ventricular filling pressure (15 ± 4 to 11 ± 8 mm Hg). In group II, unlike group I, cardiac output increased significantly from 5.2 to 6.3 liters/min (Table I). Atrial dysrhythmias were present in 2 of the 13 patients. The inspiratory decrease in arterial systolic pressure could be evaluated in 11. For the group, the average inspiratory decrease in arterial systolic pressure decreased significantly from 16 ± 8 to 8 ± 4 mm Hg with pericardiocentesis. Pulsus paradoxus was present in 6 of the 11 patients. In 5 of the 6 patients, the inspiratory decline in arterial systolic pressure decreased by 9 to 16 mm Hg after pericardiocentesis; in the sixth patient, the decrease was only 1 mm Hg, i.e., from 16 to 15 mm Hg. Percentage pulsus paradoxus was present in 3 patients (19, 20 and 19%), which was eliminated in each case after pericardiocentesis. The decrease in right atrial pressure after pericardiocentesis was significantly greater in group II than in group I (6 ± 4 vs 3 ± 2 mm Hg, Figure 2). The decreases in pulmonary arterial wedge pressure (4 ± 5 vs 2 ± 2 mm Hg) and reduction in inspiratory decrease in arterial systolic pressure (8 ± 7 vs 3 ± 4 mm Hg) and increases in cardiac output (1.1

± 1.2 vs 0.3 ± 0.6 liter/min) tended to be greater in group II than in group I but were not statistically significant. In the 48 group III patients, the pericardial aspirate ranged from 250 to 1,750 ml (median value 745). By definition, these patients had equilibration of both ventricular pressures with pericardial pressure. Pericardiocentesis resulted in significant decreases in intrapericardial, right atrial and pulmonary arterial wedge pressures, the inspiratory decrease in arterial systolic pressure, and a significant increase in cardiac output (Table I). Recordings of intraarterial pressure were obtained in 45 of the 48 patients in group III. Before pericardiocentesis, all but 7 of the 45 patients manifested an inspiratory decrease in arterial systolic pressure >12 mm Hg, i.e., pulsus paradoxus. Two of the 7 without pulsus paradoxus were severely hypotensive, with expiratory systolic pressures of 76 and 87 mm Hg; their percentage pulsus paradoxus was 10% in each case. In the remaining 5 patients without pulsus paradoxus, mean right atrial pressure was <10 mm Hg; the postpericardiocentesis increment in cardiac output was $<20\%$ in 4 and 22% in 1 patient. Before pericardiocentesis (Table I), right atrial and intrapericardial pressures, but not pulmonary arterial wedge pressure, were higher in group

FIGURE 2. Comparison of changes effected by pericardiocentesis in cardiac output (CO), right atrial pressure (RAP), pulmonary arterial wedge pressure (PAWP) and inspiratory decrease in arterial systolic pressure (IFASP) among the 3 groups. T symbol = standard error of the mean; NS = not significant.



III than in group I or II. Cardiac output was lower in group III than in group I. In group III, the decreases in pulmonary arterial wedge pressure (8 ± 5 mm Hg) and the inspiratory decrease in arterial systolic pressure (17 ± 11 mm Hg) and the increase in cardiac output (2.8 ± 1.5 liters/min) were significantly greater than those found in group I or group II patients (Figure 2). Although the decrease in right atrial pressure (9 ± 5 mm Hg) was significantly greater in group III than in group I, this did not reach statistical significance for group III versus group II.

DISCUSSION

Previously, we had thought that no hemodynamic changes occurred in pericardial effusion as long as right ventricular filling pressure exceeded pericardial pressure.¹ In the present study, we found that group I patients, characterized by the absence of pressure equilibration, manifested decreases in both ventricular filling pressures and the inspiratory decrease in arterial systolic pressure after pericardiocentesis. We also previously theorized that exaggeration of the inspiratory decrease in arterial systolic pressure sufficient to produce pulsus paradoxus occurred only when right and left ventricular filling pressures were equal to pericardial pressure, i.e., when both ventricles were filling against the common stiffness of the fluid-filled pericardium.¹ Our present data indicate that exaggeration of the inspiratory decline in arterial systolic pressure occurs when pericardial pressure is not equal to either ventricular filling pressure (group I patients). This finding is consistent with the findings of Wayne et al³ who described exaggerated inspiratory decreases in left ventricular ejection time in patients with pericardial effusion who did not have clinically evident hemodynamic embarrassment. In addition, the exaggeration reaches the criterion for pulsus paradoxus in many patients with equilibration of pericardial with right ventricular but not left ventricular filling pressure (group II patients).

We believe that our current data justify the following concept regarding the pathophysiology of cardiac tamponade (Figure 1, right): The normal pericardium has been shown to contribute to ventricular stiffness since pericardiectomy in experimental animals results in a reduction in ventricular filling pressure for any given volume.^{4,5} As evidenced by group I patients, accumulation of pericardial fluid in the early stages further stiffens the ventricles requiring a higher filling pressure. Pericardial pressure will increase provided the compensatory increase in venous pressures is able to maintain ventricular volume close to basal levels. The pericardial pressure increases as the volume of the total contents of the pericardium (cardiac volume and pericardial fluid) increases. At this early stage, elevated right and left ventricular filling pressures are higher than pericardial pressure (phase I). The compensatory increase in ventricular filling pressure is generally adequate to maintain normal cardiac output, but there may be a slight decrease in some cases. The inspiratory decrease in arterial pressure is exaggerated at this stage but rarely reaches a diagnostic level for pulsus paradoxus, depending on the basal value.

With increasing fluid accumulation, pericardial pressure increases more than ventricular filling pressures, equilibrating first with the right, which is usually lower than the left. At this stage (phase II), the operative stiffness of the pericardium is greater than the right ventricle but not the left. Systemic venous pressure must fill the right ventricle against a stiffness determined by the fluid-filled pericardium. Despite a further compensatory increase in systemic venous pressure, adequate ventricular filling is not maintained and cardiac output is compromised. The inspiratory decrease in arterial systolic pressure is further exaggerated compared with that in group I patients and reaches diagnostic levels for pulsus paradoxus in some but not all patients. The further increase in pericardial pressure sufficient to equilibrate with left ventricular filling pressure signals the onset of severe hemodynamic abnormalities (phase III). Compromise of cardiac output generally becomes severe and almost all patients manifest pulsus paradoxus. The revised concept is consistent with the hemodynamic changes noted in an acute animal experiment.⁶

If the compensatory increase in venous pressure is attenuated because of hypovolemia, cardiac output may be compromised in the presence of low ventricular filling pressures that are equilibrated with intrapericardial pressure, i.e., "low pressure tamponade."⁷ None of our patients had low pressure tamponade. However, we have encountered a subgroup of patients with equilibration of pericardial and ventricular filling pressures that were <10 mm Hg. In these patients, pericardiocentesis was associated with an insignificant increase in cardiac output. Studies in experimental animals have shown that the difference between right ventricular filling and pericardial pressure is small.^{8,9} If this also applies to humans, certain patients who have low ventricular filling pressures with a minimal difference between them may have apparent equalization of ventricular filling and pericardial pressure. When pericardial effusion develops in these patients, ventricular filling pressures will be apparently equilibrated with pericardial pressure even before the effusion causes a compensatory elevation of ventricular filling pressure. However, these patients, in contrast to those with hypovolemia, do not have compromised cardiac output. Thus, patients with equilibrated but low filling pressures may or may not have compromised cardiac output depending on whether the low pressure is secondary to hypovolemia.

We previously observed that pulsus paradoxus, defined as $>10\%$ inspiratory decrease in arterial systolic pressure, occurs when both ventricular filling pressures are equilibrated with an elevated pericardial pressure.¹ This hemodynamic condition suggested filling of both ventricles was taking place against the common stiffness of the fluid-filled pericardium. In this state, both ventricles will fill to the same degree as long as the filling pressures remain equal. However, transient disturbances in this equilibrium caused by respiratory changes in intrathoracic pressure alternately favor left and right ventricular filling leading to pulsus paradoxus. During inspiration, pulmonary venous pressure decreases below systemic venous pressure, whereas the reverse holds true during expiration. We thus believed elevation and equil-

ibration of ventricular filling pressures with pericardial pressure were necessary conditions for the production of pulsus paradoxus associated with pericardial effusion. Although every patient with elevated ventricular filling pressures which were equilibrated with pericardial pressure manifested pulsus paradoxus, a new finding in the present study was an exaggerated inspiratory decrease in arterial systolic pressure in patients who did not fulfill all these hemodynamic criteria. Pulsus paradoxus was a frequent finding in patients whose right ventricular filling pressure was equilibrated with pericardial but not left ventricular filling pressure. Only an occasional patient without any pressure equilibration had evidence of pulsus paradoxus. However, even in this group of patients, the inspiratory systolic pressure decline was exaggerated. The mechanism of pulsus paradoxus is complex and remains elusive. The following explanation appears to be reasonable based on current data: With inspiration, intrathoracic pressure decreases, facilitating a greater flow into the right heart chambers from the extrathoracic systemic veins. An important mechanism in altering flow to the left heart may be ventricular interaction.¹⁰⁻¹² Increased right heart filling tends to raise pericardial pressure and increase the impedance to left ventricular filling. This interaction may be partly responsible for the normal inspiratory decrease in arterial systolic pressure. This interaction may be further exaggerated as the ventricles are increasingly stiffened by pericardial effusion, and pericardial pressure equilibrates with right ventricular filling pressure as in group II patients. This interaction may be maximal when elevated pericardial pressure equilibrates with both left and right ventricular filling pressures as in group III patients. Equilibration of pressures on either side of the ventricular septum may convert this normally left ventricular structure into a neutral structure (i.e., it may become part of either the right or left ventricle depending on the filling pressures). With expiration, when pulmonary venous and left ventricular filling pressures are transiently higher than right ventricular filling pressure, it is concave toward the left ventricle. With inspiration, when intrathoracic pulmonary venous pressure transiently decreases below right ventricular filling pressure (extrathoracic systemic venous pressure), the septum may bulge toward the left ventricle with a concavity

toward the right ventricle. This contributes to the capacity of the right ventricle at the expense of left ventricular volume. Thus, with the addition of the "septal component," the interaction between the ventricles will be most exaggerated when ventricular filling pressures are equilibrated. This explanation is consistent with the echocardiographic observations of an inspiratory septal shift in patients with pulsus paradoxus secondary to pericardial effusion.^{13,14} In addition, accumulation of fluid after initial equilibration of ventricular filling pressures may further exaggerate the pulsus paradoxus primarily because of compromised filling from increased stiffness. In severe tamponade, when left ventricular filling is severely compromised, the inspiratory bulge of the septum may almost totally obliterate the left ventricular cavity. This may result in minimal or no stroke volume and an absent arterial pulse.

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Transesophageal Echocardiography in Critically Ill Patients

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The feasibility, safety and clinical impact of transesophageal echocardiography were evaluated in 51 critically ill intensive care unit patients (28 men and 23 women; mean age 63 years) in whom transthoracic echocardiography was inadequate. At the time of transesophageal echocardiography, 30 patients (59%) were being mechanically ventilated. Transesophageal echocardiography was performed without significant complications in 49 patients (96%), and 2 patients with heart failure had worsening of hemodynamic and respiratory difficulties after insertion of the transesophageal probe.

The most frequent indication, in 25 patients (49%), was unexplained hemodynamic instability. Other indications included evaluation of mitral regurgitation severity, prosthetic valvular dysfunction, endocarditis, aortic dissection and potential donor heart. In 30 patients (59%), transesophageal echocardiography identified cardiovascular problems that could not be clearly diagnosed by transthoracic echocardiography. In the remaining patients, transesophageal echocardiography permitted confident exclusion of suspected abnormalities because of its superior imaging qualities. Cardiac surgery was prompted by transesophageal echocardiographic findings in 12 patients (24%) and these findings were confirmed at operation in all.

Therefore, transesophageal echocardiography can be safely performed and has a definite role in the diagnosis and expeditious management of critically ill cardiovascular patients.

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Transthoracic echocardiography is frequently unsatisfactory in the intensive care unit, especially when the patient is connected to life-support devices or has recent surgical wounds that limit optimal ultrasound windows. Transesophageal echocardiography, not affected by these constraints, can predictably provide high-quality tomographic images of the heart and the thoracic aorta in nearly every patient.¹ To date, only limited discussion of this important application of transesophageal echocardiography has been published. We report the feasibility and safety of transesophageal echocardiography and its clinical impact in critically ill patients from our first-year experience with this procedure.

METHODS

Patients: From November 1987 to December 1988, 580 patients underwent transesophageal echocardiographic examinations outside the operating room. Of these, 51 patients (9%) were classified as critically ill (in an intensive care unit): 25 in the coronary care unit, 15 in the surgical intensive care unit and 11 in the medical intensive care unit. Twenty-eight patients were men and 23 were women (mean age 63 years, range 18 to 85). In each, transthoracic echocardiography was nondiagnostic, of suboptimal quality, or impossible because of inaccessibility of precordial ultrasound windows. At the time of transesophageal echocardiography, 30 patients (59%) were being mechanically ventilated.

Transesophageal echocardiography: Transesophageal echocardiography was performed with a Hewlett-Packard transesophageal probe with a 5-MHz transducer as described.¹ In each patient, 10% lidocaine spray was used for local anesthesia and intravenous glycopyrrolate (Robinul®, 0.2 mg) for secretion control if necessary. Unless the patient was already sedated, midazolam (Versed®, 1 to 7 mg) was administered intravenously. Two patients on mechanical ventilation were given pancuronium bromide for severe agitation. Subacute bacterial endocarditis prophylaxis was administered for patients who had prosthetic valves without suspected endocarditis. Initially, the nasogastric tube was removed before the study. However, after several patients had been examined, the transesophageal probe was inserted without removing the nasogastric tube and adequate images were obtained.

The severity of valvular regurgitation was assessed qualitatively by visualizing the width, extent and dura-

tion of the regurgitation jet on color-flow imaging and was classified as severe or nonsevere (mild to moderate).² Patients' records were reviewed retrospectively to determine their subsequent clinical course.

RESULTS

Feasibility and safety: No clinically significant complication was noted in 49 of 51 patients (96%). One patient with severe ischemic left ventricular dysfunction experienced increasing respiratory difficulty and an increase in pulmonary artery pressure (systolic, from 55 to 74 mm Hg). The transesophageal probe was withdrawn promptly without imaging and the patient's hemodynamics returned to the baseline immediately. In the other patient, who had persistent hypoxemia (partial arterial oxygen pressure, 66 mm Hg; oxygen saturation, 89%) on mechanical ventilation with 100% oxygen, worsening of oxygen desaturation (arterial oxygen saturation, 64%) developed after 5 minutes of diagnostic transesophageal echocardiography.

Indications and findings: The main indication for transesophageal echocardiography was unstable hemodynamics. Twenty-five patients (49%) had shock, hypotension or pulmonary edema, of whom 10 had a recent myocardial infarction and 7 underwent operation (4 cardiac and 3 vascular). Transesophageal echocardiography diagnosed the following abnormalities: severe mitral regurgitation in 9 patients (due to papillary muscle dysfunction in 5, papillary muscle rupture [Figure 1] in 2, periprosthetic mitral regurgitation in 1 and flail bioprosthesis in 1); severe left ventricular dysfunction in 4, right ventricular infarct in 2 (1 patient with concomitant right-to-left shunt through the patent foramen ovale [Figure 2]); hypovolemic state in 3 patients with hyperdynamic small left ventricular cavity; critical aortic stenosis in 1 patient with pulmonary edema after abdominal aortic aneurysm repair; mediastinal hematoma

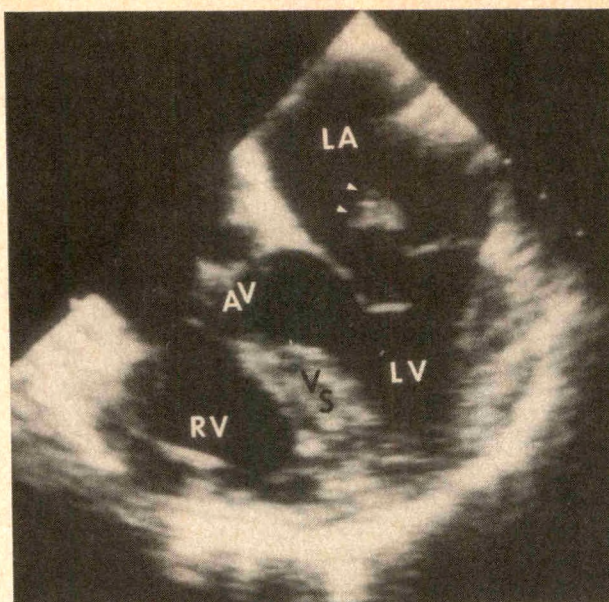


FIGURE 1. Systolic still frame of transesophageal 4-chamber view, demonstrating papillary muscle rupture. Ruptured head of the papillary muscle (arrowheads), attached to the posterior mitral leaflet, flails into the left atrium (LA). The mitral valve coaptation is grossly inadequate, allowing massive mitral regurgitation. AV = aortic valve; LV = left ventricle; RV = right ventricle; VS = ventricular septum.

in 1 patient after recent repair of proximal aortic dissection; dehiscence aortic homograft valve in 1 patient; and postinfarct ventricular septal defect (Figure 3) in 1 patient. Eight of these patients underwent cardiac surgery, which confirmed transesophageal echocardiographic findings in all cases.

Ten patients were evaluated for vegetation or ring abscess. Transesophageal echocardiography demonstrated a soft tissue mass posterior to the aortic prosthesis

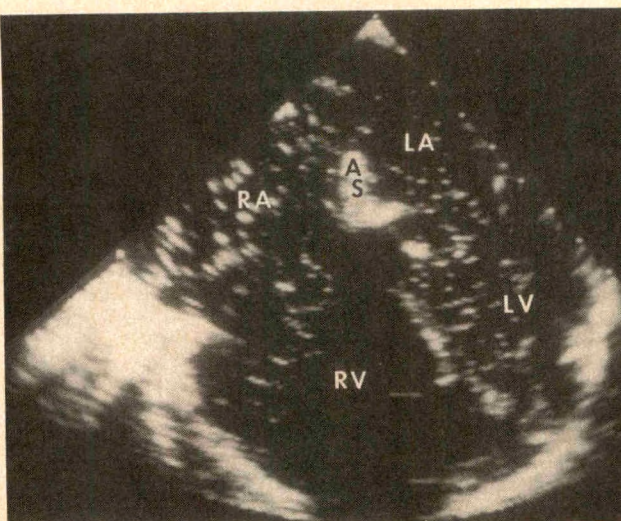
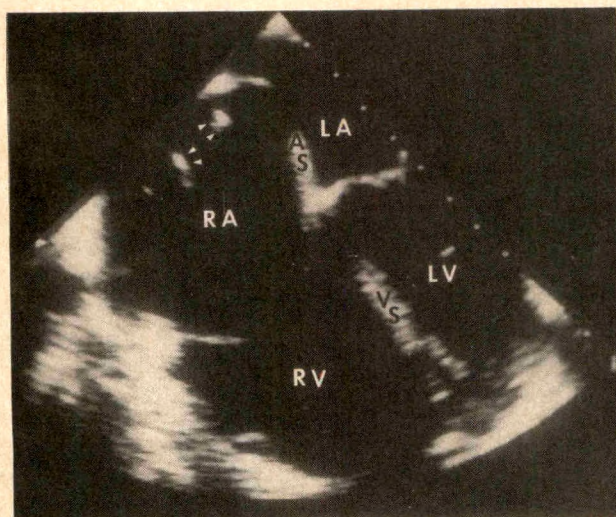


FIGURE 2. Left, transesophageal 4-chamber view, demonstrating right ventricular (RV) infarct. Right cardiac chambers are dilated and atrial septum (AS) bulges toward left atrium (LA) because of high right atrial (RA) pressure. Swan-Ganz catheter and temporary pacemaker wires are seen in right atrium (arrowheads). Right, because of persistent hypoxemia despite oxygen therapy, right-to-left shunt was suspected. Contrast agent injected into the right atrium appears immediately in the left cardiac chambers, confirming right-to-left shunt across a patent foramen ovale. LV = left ventricle; VS = ventricular septum.

sis in 2 patients and vegetations on mitral (Figure 4) and aortic prostheses in 1 patient each. Based on these findings, the first 3 patients underwent operations at which an infected hematoma within an aortic false aneurysm, aortic ring abscess and mitral prosthetic vegetation were found, respectively.

Six patients were evaluated for cardiac contusion. Five were brain dead and considered as heart donors. Transesophageal echocardiography revealed findings

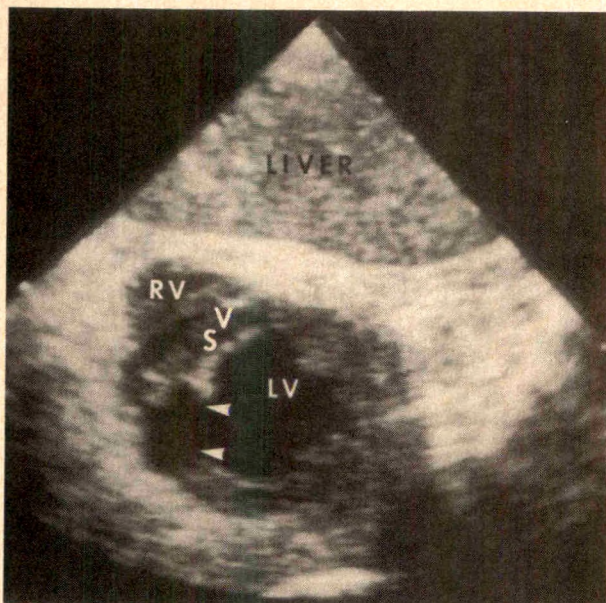


FIGURE 3. Transgastric view, demonstrating postinfarct ventricular septal defect. A large tear (arrowheads) in the antero-septum is clearly shown. LV = left ventricle; RV = right ventricle; VS = ventricular septum.

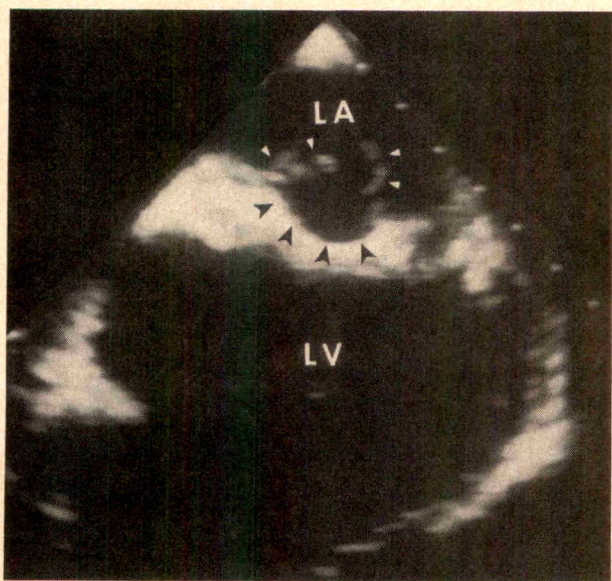


FIGURE 4. Close-up view of a Starr-Edwards mitral prosthesis by transesophageal echocardiography in a 16-year-old patient with sepsis. Large mobile linear structures (white arrowheads) are attached to either side of the sewing ring (black arrowheads), the typical appearance of vegetation. LA = left atrium; LV = left ventricle.

consistent with right ventricular contusion (dilated right ventricular cavity and akinetic free wall)³ in 1 and akinetic ventricular septum and anterior wall in another patient. Both patients were rejected as donors, and postmortem examination showed right ventricular contusion and anterior myocardial infarction due to left anterior descending coronary artery thrombosis, respectively.

Ten patients were referred for suspected aortic dissection (6 patients), cardiac source of embolus (3 patients), or abnormal left ventricular contour on transthoracic echocardiography associated with persistent chest pain after myocardial infarction (1 patient). Transesophageal echocardiography demonstrated a dissection of the descending aorta, nonvascular mediastinal mass (subsequently diagnosed as a metastatic tumor), left atrial thrombus, and contained left ventricular free-wall rupture in 1 patient each. The free-wall rupture was surgically repaired successfully.

DISCUSSION

Feasibility and safety: The intensive care unit environment imposes restriction on the imaging ability of transthoracic echocardiography. In this setting, transesophageal echocardiography offers an alternative imaging window to the heart and the thoracic aorta. However, transesophageal echocardiography is a semi-invasive procedure, and there is concern about performing such a procedure in a critically ill patient. Our experience demonstrated that transesophageal echocardiography could be performed with a low risk in the critically ill patient, although our complication rate of 4% is higher than the complication rate (<1%) reported by others^{4,5} in awake patients. This difference may be related to the fact that the mild changes in hemodynamics during the transesophageal echocardiographic examination⁵ may produce clinical deterioration in these patients with marginal hemodynamic status. Therefore, transesophageal echocardiography should be performed by a cardiologist experienced in managing potentially life-threatening cardiovascular situations, and we recommend continuous blood pressure and heart rate monitoring as well as oxygen saturation during the procedure.

Clinical impact of transesophageal echocardiography: Critically ill patients, especially when hemodynamically unstable, require prompt diagnostic evaluation. Transesophageal echocardiography is the only diagnostic procedure now available that can be performed at the bedside, can predictably image the heart and the aorta, and can provide blood flow information. All these are achieved without moving the patient or injecting contrast medium. Various cardiac problems responsible for hemodynamic deterioration were readily diagnosed by transesophageal echocardiography, such as severe mitral regurgitation due to papillary muscle dysfunction or rupture, ventricular septal defect, severe aortic stenosis, hypovolemic state and ventricular dysfunction. It has also been reported that transesophageal echocardiography was useful in detecting localized hematoma compressing the right cardiac chambers in hypotensive patients postoperatively.⁶

Transesophageal echocardiography was also valuable in the evaluation of prosthetic valvular dysfunction, detection of vegetation, and aortic dissection as reported by others.⁷⁻⁹

Donor heart failure is a recognized cause of mortality after cardiac transplantation.¹⁰ Two of 5 patients in this study who seemed to be suitable heart donors clinically were found to have significant right or left ventricular wall motion abnormalities. Such clinically unsuspected cardiac abnormalities may contribute to donor heart failure after transplantation.

Of 51 critically ill patients, 12 (24%) underwent cardiac surgery primarily on the basis of transesophageal echocardiographic findings. When the transesophageal echocardiographic examination was negative, the cardiac abnormalities suspected could be excluded confidently because of the superb images obtained.

For echocardiography to be a complete diagnostic procedure, it needs to provide predictable cardiac images of convincing clarity so that definitive planning of patient management is possible without further tests to confirm the echocardiographic findings. In this regard, transesophageal echocardiography is superior to the transthoracic approach, especially in the critically ill patient with a limited precordial ultrasound window.

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The Developmental Phase of Modern Coronary Artery Surgery

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Because of the many questions related to the developmental phase of modern coronary artery surgery that my colleagues posed during my participation in international meetings in recent years, I decided to enlarge a previous study published in 1983¹ and present in detail the major events that occurred when I left Argentina—my home country—and joined the Cleveland Clinic team in Ohio in 1962.

I graduated from the Medical School at the University of La Plata. Since my training as a resident in general surgery, I had been attracted by thoracic surgery. As a consequence, I traveled on Wednesdays to the Rawson Hospital in Buenos Aires, where Enrique and Ricardo Finochietto had organized a postgraduate program, mainly to get acquainted with lung and esophageal resection. After I finished my residency early in 1949, those trips became a weekly duty. We were lucky to have 2 outstanding surgeons in La Plata: Professor Federico Christmann and Professor José María Mainetti. I started my training with the latter, an energetic, unusually ambidextrous and skillful surgeon who became my master. I lived in the University Hospital, in a small room, and thought only of my work and the teaching career I chose early on as a student teaching assistant in anatomy. But my destiny, for many reasons, led me to become a country doctor in a small village in the southwest of the dry pampas in May 1950.

With tremendous effort, saving every penny—I come from a low-to-middle class family; my father was a carpenter, my mother a dressmaker—I was able to build up a small clinic with 1 operating room and an x-ray machine. For the first time, surgery was performed in that rural area; emergency operations became my principal work. My only brother—Juan José—also a surgeon, joined me 2 years later. From then on, the broad spectrum of general surgery engaged most of our time, because ours was the only properly equipped and organized clinic for more than 150 kilometers.

Even though I was far from my University, I made regular trips to La Plata and we received the most important medical journals. The early contributions in cardiovascular surgery made a great impression on me in

the early fifties, and though I was satisfied with our work in the countryside, in 1960 I began to cherish the idea of travelling to the United States to be trained in thoracic and cardiovascular surgery. In 1961 I talked to Professor Mainetti, who understood how I felt and who, after one of his many trips to that country, advised me to go to the Cleveland Clinic. Not too many doctors in Argentina knew about the Cleveland Clinic in those days. Consequently I asked: "Why the Cleveland Clinic?" He answered very quickly: "They have one of the best cardiology departments. They are far advanced, mainly in the cardiac laboratory, because of the work of Mason Sones. Besides, they have an excellent research department, where Kolff is working, and I saw Effler in the operating room and he is an excellent surgeon." Dr. Mainetti wrote to his friend, George Crile, Jr., and at the beginning of February 1962 I traveled to Cleveland with my wife.

I will never forget my 12 years in Jacinto Aráuz, the village where we worked. They taught me many things, but the most important thing I learned is that the patients we treat in practice should be treated with honor, and that they deserve our love and, oftentimes, our compassion.

After my arrival in Cleveland I went to see Dr. Crile. We had a friendly talk and I was very impressed with his personality. Later on he became one of my best friends at the Clinic. I had always admired his humanistic idealism. He telephoned Dr. Donald Effler and after a few minutes I was in Dr. Effler's office with some fear in my soul. I explained the reason for my trip and emphasized that I was ready to work with dedication and responsibility. I did not have the proper requirements—mainly, the Educational Council Foreign Medical Graduate examination—and he made it clear that I could only be accepted as an observer, without any payment. I explained that I had been able to save some money and was not asking for a salary, only a place to learn. He sent me to the educational department to be registered. My happiness ended when the director gave me a hard time. Shortly before, a fellow from Argentina had been admitted to work in the research department; he had signed a contract for 1 year and had disappeared within the first 2 months, without giving notice, to join another hospital in the south of the state. As a consequence, the director told me that he did not want any other doctor from that "wild country." The interview became very sour and finally I stood up and told him that I was sorry about the circumstances but could not tolerate his insults to Argentina any longer. I thought: "This is the end of my dream."

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However, I went back to see Effler; I explained what had happened. To my surprise he said: "Forget all about it. Tomorrow you will start work at 8 o'clock." And this is the way I was admitted to the Cleveland Clinic. I had to buy my own white coats because, not having been accepted officially by the educational department, only the greens for the operating room were available for me.

Besides Effler and his partner, Dr. Larry Groves, the members of the Department of Thoracic & Cardiovascular Surgery were: a senior resident, Dr. Niall Scully, a junior resident, Dr. Alfonso Parisi, and sometimes a rotating fellow from general surgery. Most of the daily work was lung resection, esophageal repair or resection, and mediastinal tumors. Only 3 or 4 open-heart surgeries, mainly relating to congenital diseases, were performed per week. Within 2 weeks, Effler invited me to scrub up and made me the second assistant in a left pneumonectomy. From then on I assisted him and Groves at every opportunity. I placed Foley catheters, pushed beds back and forth to the intensive care unit, helped the anesthetists and Rose Litturi, who was in charge of the pump equipment, clean, silicone and set the enormous extracorporeal machine with a Key-Cross oxygenator and electronic flow meter. In short, I did everything possible to show my gratitude.

THE BEGINNING

Just before my arrival at the Cleveland Clinic, two important events had occurred. On January 5, 1962, Effler and his associates had been successful in overcoming a severe obstruction at the left main coronary artery² using the patch graft technique described by Senning.³ Sones, on January 12, examined a patient operated on by Vineberg in Canada in 1946 and used selective opacification of the left mammary artery to reveal that collateral circulation arising from a systemic artery implanted in a small tunnel was sufficient to diminish the myocardial perfusion deficit in the territory perfused by the anterior descending branch of the left coronary artery. His finding was repeated in March in another patient, operated on by Bigelow.

Right from the start I was drawn to the work of Mason Sones, Earl Shirey and their colleagues, who performed hundreds of top quality cine coronary angiograms down in the basement.⁴ Studies of such precision and skill were at that time only available in the Cleveland Clinic and, furthermore, were systematically stored. Sones' department was called B₁₀ and it was there that I spent most of my free time after finishing the day's work in the Department of Thoracic & Cardiovascular Surgery. I had rented a small apartment just across the street in an old building with an amusing name—"Palais Royal." Living so close to the Clinic, I avoided traveling through the streets and roads, which are covered with snow most of the winter in the Ohio Great Lakes area. This way, I was able to prolong my activity late into the evening and sometimes even into the night.

Slowly and steadily, with the help of the fellows working in B₁₀, I started learning how to read cine coro-

nary angiograms. I found the doors of Sones' office permanently open, learned that it was his habit to wear a white undershirt and that he was always willing to exchange ideas with his associates and the innumerable visitors from all over the world who came to watch him work. With humility I asked for his advice in interpreting some of the movies that were difficult for me because of my lack of experience. From then on we developed a deep and everlasting friendship.

After a few months it became clear that 2 distinct groups of patients could be categorized: (1) those with diffuse disease that involved most of the coronary branches, very often with collateral vessels between them, and (2) those with select, localized obstructions, mainly at the proximal segments of the coronary branches, with good distal runoff. The analysis of the cine left ventriculograms showed a definite correlation between the severity of coronary arteriosclerosis and the state of the heart muscle. At that time only the right anterior oblique projection was used. Later on, because of my daily observation at the operating room, mainly of patients with ventricular aneurysm and poor ventricular contraction, I suggested to Mason that the left anterior oblique view was necessary to visualize the septum and lateral wall. Since then, both projections have become mandatory for the analysis of the entire left ventricle, to clarify the proper indication and operative approach.

I studied for the Educational Council Foreign Medical Graduate examination mainly on weekends and have to confess that it was difficult to sit still for so many hours, reviewing anatomy, physiology, biochemistry, after so many years had passed since I finished medical school. But I knew it was worthwhile and very often I went to the library to become familiar with books and journals of our field.

Surgical attempts under the leadership of Effler were applied to most patients following Vineberg's ideas.⁵⁻⁷ The patch repair technique was used in a select group and, as our experience accrued, so was resection of scar tissue and ventricular aneurysm, when indicated.⁸

Indirect myocardial revascularization: The left internal mammary artery was prepared through a left posterolateral thoracotomy, following Vineberg's technique, with meticulous dissection to avoid any damage. We found that, if we left a sponge impregnated, with papaverine attached to it, while we prepared the tunnel, spasm was avoided and the artery lumen enlarged. The internal mammary artery was applied on the anterolateral wall of the left ventricle. Dr. David Fergusson, who arrived from South Africa to join Sones' department, became an expert in direct visualization of the mammary arteries in the cardiac laboratory. He analyzed the postoperative studies he and the other members of B₁₀ had performed and found that the patency rate and the degree of connection with the coronary circulation were directly related to the severity of the obstruction and the presence of collateral circulation. The overall results were gratifying.⁹ Our work increased steadily. After passing the Educational Council Foreign Medical Grad-

uate examination, I became a regular junior fellow in 1963 and the chief resident in 1964.

In 1965 Effler invited Sewell to operate on a patient in our hospital, and I helped him. His approach—the pedicle technique—allowed the surgeon to work far from the artery and consequently the dissection was done in a short time and with less trauma.¹⁰ The drawback was that the tunnel had to be made with a bistoury blade in order to place the pedicle in the heart muscle. As a consequence, we combined the Vineberg and Sewell techniques. After the dissection was done, the mammary artery in the distal segment was free of all the surrounding tissue and only that portion was placed inside the tunnel, which was made in the classical fashion of the original Vineberg operation. This approach became known to us as the Vineberg-Sewell technique.

The midline anterior thoracotomy became a routine procedure for most of our open-heart operations and, very often, when I lifted the sternum up to place the Finochietto retractor, or, at the end of the operation to control some bleeding, the mammary arteries were right there. I could see and palpate them. In 1965 I dissected some portions, mainly at the level of the fourth and fifth interspaces. I discussed the idea of using both mammary arteries with Mason several times, but somebody told him that necrosis might occur if the sternum was deprived of that blood supply. Reviewing the anatomy, I thought it logical to think this a senseless warning. Finally, in 1966 (I was now a staff member of the Department of Thoracic & Cardiovascular Surgery), I dissected both mammary arteries and implanted them in the left ventricle: the right, parallel to the anterior descending branch, and the left, on the lateral wall in a tunnel underneath the branches of the circumflex coronary artery and the distal branches of the right coronary artery.^{11,12} I performed 38 consecutive procedures without any mortality, possibly because we selected the patients very carefully.

The dissection was done with routine instruments and with the assistance of one of the fellows who, by the end, was always very tired after holding the sternum up with both hands. Consequently, I designed a special self-retaining retractor,¹³ which, with some modifications, is used today in cardiovascular centers all over the world to dissect the internal mammary artery for internal mammary artery coronary anastomosis. I also designed the instruments so that we could make the tunnel in the anterolateral and diaphragmatic wall of the left ventricle without distorting the heart. We never used extracorporeal circulation to perform a double internal mammary implant. We learned that by holding the heart very gently ("as a lady," I used to tell the residents), we were able to avoid arrhythmias and hypotension.

When Vineberg learned that we were using this new approach, he visited the Cleveland Clinic with some frequency and we exchanged ideas between operations. From then on we became close friends. When I returned to Buenos Aires he wrote me now and then, until his death on March 26, 1988. An extensive discussion of Vineberg's original ideas is found in the book¹⁴ I wrote in 1970 (see page 67 of reference 14). I still believe that

our new approach was a good way to ameliorate myocardial perfusion deficit. The most significant demonstrations were obtained in some patients whose repeat catheterizations showed that their left coronary arteries were totally occluded at the ostium and that their left ventricles were perfused by both implants by a sponge of collateral circulation.

We summarized the experience we had at the Cleveland Clinic with the indirect approach at the annual meeting of the American Association for Thoracic Surgery in 1967.¹⁵ Thinking back, I sometimes believe that we were expecting miracles, because we knew that several months were required to develop connections between the systemic artery and the coronary artery tree. Cardiologists referred us patients with intractable angina, impossible to control even under the strictest medical regimen. They demanded our help because the cineangiograms revealed severe obstructions at the left main trunk level or severe proximal obstructions in the anterior descending and circumflex branches of the left coronary artery without collateral vessels.

When we reviewed the first 585 patients who underwent bilateral internal mammary implant, we found that 73 (12.4%) had left main trunk obstruction; 14 of the 43 patients who died after the operation belonged to that group, and 71.1% of the perioperative myocardial infarctions were related to obstructions of the anterior descending coronary territory.

The midline anterior thoracotomy helped us accomplish combined simultaneous procedures since 1966. We performed ventricular aneurysmectomy, valve repair or valve replacement with concomitant single or double implants.¹⁶

Direct myocardial revascularization: As I have mentioned, the direct approach arose in January 1962 with the patch graft technique. Patients were carefully selected and the results were gratifying for localized obstructions, mainly those on the right coronary artery, with an acceptable operative mortality (10.5% of 142 patients). Mortality was extremely high, however, in patients with left main trunk obstruction: 11 deaths in 14 patients. We tried different operative approaches,¹⁴ including transection of the pulmonary artery (see page 44 of reference 14). I was convinced and still do believe that the heart muscle of the left ventricle in patients with severe disease at the left main trunk level functions under severe chronic anoxia. Though the aorta was cross-clamped (the only way to approach the left main trunk) for approximately 20 minutes, it was enough to alter the myocardial cell metabolism to an irreversible state. It is worthwhile to mention that cardioplegia was not available at that time. These poor results were the reason for the application of the double mammary implant in patients with left main trunk obstruction, certainly our worst enemy.

In those years I used to go to the operating room with both the thrill of challenge and with fear in my soul. Sometimes, when the kidney transplantation team was desperately looking for a donor and they saw in the surgical schedule that I was ready to approach that kind of patient once more, they would come and ask permission to perform a crossmatch before the operation.

One morning, just before we were getting ready for a left main trunk reconstruction, one of the residents, a fervent Catholic, told me of his inner struggle between his duty as a surgeon and his religious sentiments, and informed me that he did not wish to participate in the operation because he felt guilty. After the operation we had a long talk. I told him that I too was a Catholic but as a surgeon I felt that I had to make every effort to help those patients with the most difficult coronary artery disease. I informed him that he had chosen a very hard career in becoming a surgeon and that he should think well in advance of the consequences. A surgeon's life means assuming responsibility for the risk that accompanies his decision to operate. The deaths associated with surgery are personal and the surgeon must endure their burden as long as he lives. He must never, of course, consider his patients as experimental subjects or as objects upon which to perfect his preferred treatment. I ended by saying that I did not believe we were breaking those ethical rules and that we were genuinely searching for a solution to an extremely difficult problem. The review of 13,000 cineangiograms performed by Sones and associates showed that only 32 patients survived total occlusion of the left main coronary artery. Of course, all of them had diffuse collateral vessels originating in the right coronary artery.

As our experience grew, longer patch reconstructions were performed, but the postoperative cine coronary angiograms showed that there was a direct relation between the extent of the repair and the rate of postoperative thrombosis. The longer the repair, the greater the failure. This was a result of the coronary artery being effectively untouched, and so its inner surfaces retained irregularities that could disturb the flow pattern, leading to the production of thrombosis and consequent occlusion.

Early in 1967 I thought that the use of the saphenous vein could solve the problem. There was enough experience in peripheral and renal artery reconstruction with that kind of graft at the Cleveland Clinic. Why not at the coronary level? I discussed the idea with Mason and some of his associates and we decided that at the beginning we should try grafting in the right coronary artery and that the patient must have a totally occluded vessel with the distal segment visualized by collaterals. If the graft occluded, the patient would suffer no harm. The first operation was performed in May 1967 on a 51-year-old lady who had been catheterized by David Fergusson. The proximal and distal segments of the totally occluded right coronary artery were reconstructed with a segment of saphenous vein and 2 end-to-end anastomoses. Sones was very anxious to restudy the patient and did so 8 days later. He called me and as soon as I finished one of the operations I went to the cardiac laboratory. Mason showed me the film on the Tage-Arno. I had very rarely seen him so happy. The right coronary artery had been totally reconstructed and there was an excellent distal runoff. A few days later he took a 16-mm movie of the pre- and postoperative studies to a meeting in West Germany.

Very early in our experience we realized that the interposed technique presented significant limitations. A

bypass from the anterolateral wall of the aorta was done on the fifteenth patient, as pointed out in page 337 of my first publication.¹⁷ Because bypasses to the right coronary artery were performed at the beginning, the distal anastomosis was done end-to-end with the advance knowledge that the diaphragmatic distribution of the right coronary artery was the most important segment, supplying blood to the right ventricle and a portion of the left ventricle in a dominant right coronary artery circulation. We preferred to direct the total flow to the diaphragmatic posterior descending and atrioventricular branches. We switched to the end-to-side anastomosis later on. We therefore extended the technique to the left coronary artery distribution.¹⁸ At the beginning we went slowly, because we did not know of any previous clinical application and were concerned with the late evolution of the graft, mainly with thrombosis and dilatation. The fact that the proximal anastomoses were placed on the anterolateral wall of the aorta a couple of centimeters above the natural ostium led me to believe that the graft would remain patent because it would follow the natural coronary flow pattern. Mason was not so enthusiastic. He would say: "Let's see if they plug at three months. We must carefully select the patients and wait until we have the postop cineangiogram."

1968

The important landmarks achieved in 1968 were the result of a team effort based on the high-quality cineangiograms performed by Sones and colleagues in B₁₀, the pioneer work by Proudfit et al¹⁹ on the natural evolution of patients with coronary arteriosclerosis under medical treatment, which allowed us to screen the proper surgical candidates and compare the operative results, and the operations performed in the Department of Thoracic & Cardiovascular Surgery under the leadership of Effler. I will always thank him for giving me total freedom to work and for encouraging the development of new ideas.

As a consequence we combined:

1. The coronary artery bypass technique with left ventricular reconstruction (aneurysmectomy or scar tissue resection) following the ideas originated in 1966.¹⁶
2. Coronary artery bypass surgery with concomitant valve replacement, because cine coronary angiograms were regularly made of patients with valvular diseases.¹⁴
3. The application of the bypass operation to the left coronary artery distribution (see page 47 of reference 14).¹⁴ The first operation was performed on a patient with severe obstruction of the left main trunk and minimal changes on the left anterior descending and circumflex branches. A single bypass to the proximal segment of the left anterior descending branch showed excellent perfusion of the entire left coronary artery in the postoperative study. Left main artery disease had been defeated. This was one of the most gratifying rewards I have ever had in my life as a surgeon after many years of suffering and sweating.
4. Emergency bypass surgery in impending infarction and acute infarction.²⁰ The available literature, mainly the experimental contributions of Cox et al,²¹

convinced me that, if good oxygenated blood was available in the early hours of a myocardial infarction (and certainly the bypass graft was able to supply it), the muscle could recuperate. In those days our patients waited for 2 or 3 months to be operated on. Our facilities were limited because we only had 3 operating rooms and those with threatening obstructions stayed across the street at the Bolton Square Hotel. As soon as we had a cancellation in our daily work they were immediately admitted and operated on.

I used to arrive at the Cleveland Clinic around 7 o'clock in the morning. One day, one of the residents told me that a patient, in whom a previous cine coronary angiogram showed a subtotal occlusion in the proximal segment of a large anterior descending artery, was in trouble at the Bolton Square Hotel. We quickly went to see him and found that at around 6 A.M. he had developed severe chest pain that had lasted for approximately half an hour. It was very clear that he had suffered an acute myocardial infarction. He was sweating, with typical dusky color in his fingers because of poor peripheral circulation; he was dyspneic (the lungs were full of rales) and hypotensive. The electrocardiogram confirmed an anterolateral myocardial injury.

I ran to B₁₀ and asked Mason for permission to operate (he had performed the cineangiogram). As usual he was concerned, because he respected and loved his patients. I explained in detail the principal major experimental contributions in the literature and that I did not consider my suggestion an adventure; I thought there was already enough evidence accumulated to favor the use of the coronary bypass graft as the solution to this problem. On the other hand, we knew from the cineangiogram that this patient was in the middle of a large anterolateral myocardial infarction. Even if he survived, he would lose a significant portion of the left ventricle. Mason finally agreed.

I rushed the patient to the operating room and the whole team moved quickly. He was anesthetized in a few minutes. I opened the chest and, as was the case many times in emergency operations, the patient was cannulated in a few minutes. When we opened the pericardium, the anterolateral wall of the left ventricle did not contract, and it had a bluish color. A vent on the left ventricle through the left atrium was mandatory to decompress the heart. The operation went smoothly. As soon as we finished the proximal anastomosis, red oxygenated blood went to the anterior descending coronary artery and its branches, the anterolateral wall started to contract and, after approximately 25 minutes of support with the heart-lung machine, the patient was off bypass. The blood pressure improved and remained within normal limits. The next day he was extubated and had an uneventful recuperation. He was restudied within 10 days and the cine left ventriculogram demonstrated a small, localized area of deterioration on the anterolateral wall. The left ventricular end-diastolic pressure was normal. This was indeed a gratifying experience.

We published the first paper in *The American Journal of Cardiology*,²⁰ where we reported 18 impending infarctions and 11 acute infarctions. In one of the con-

clusions we said: "When operations are performed within 6 hours of an acute myocardial infarction most of the heart muscle can be preserved." It still surprises me today—only 11 patients were operated on. We concluded: "Cardiovascular surgeons are at the threshold of a more aggressive surgical approach in the treatment of patients with acute coronary insufficiency. Further clinical experience will be necessary to substantiate the views presented here."

When I wrote the monograph in 1970,¹⁴ in the chapter dedicated to this subject I predicted: "Personally, I do hope that in the future, patients with acute myocardial infarction will be treated in the same way as those patients with a 'dead leg' from acute thrombosis or embolization of the peripheral circulation are now treated. Those patients are admitted under the direction of a combined surgical and medical team. Emergency angiography is performed and surgical intervention is routinely performed, with total recovery in a significant number of them. Further clinical experience will be necessary to substantiate this point of view." This has become a reality in some patients with the introduction of fibrinolytic agents in combination with surgery or angioplasty in the acute or subacute phase of a myocardial infarction.

5. In December, I performed a double bypass to the right coronary artery and anterior descending branch of the left coronary artery, thus opening the door to multiple bypass approaches in patients with multiple vessel obstructions. It is worth mentioning that I had previously done a double reconstruction with the interposed technique in March 1968 (see page 54 of reference 14).¹⁴

I summarized the advances we made in the operative technique in a paper accepted for publication in *The Journal of Thoracic and Cardiovascular Surgery* in December 1968.¹⁸ By the end of that year, the largest series of patients in the world (171) had been accumulated.

1969 TO 1970

In 1969 we gained more confidence as the promising results, from continuous observation, of long-term survival, were compiled by Sheldon et al^{22,23} in detail, with effort and dedication. The excellent contributions by Milwaukee's Johnson et al,²⁴⁻²⁷ showing that bypasses could be placed in the distal segments of the coronary artery distribution, widened the scope of indications for coronary bypass surgery.

By December 1969, we had operated on 570 patients and this surgical experience was presented at the Sixth Annual Meeting of the Society of Thoracic Surgeons in Atlanta.²⁸ For the first time we reported that the coronary arteries—mainly the anterior descending artery—could occasionally be found inside the myocardial muscle, and described the proper technique to overcome the problem. As is customary in our work, we learned this lesson by suffering in the operating room. I will never forget the day when I could not find the coronary arteries that were clearly visualized in the cineangiogram. I called Mason, showed him the heart (we were already

in total bypass), and told him that I could not see the coronary arteries and that perhaps he had given me a different cine study. He refused to accept my suggestion. Together we went to review the film again (we had a Tage-Arno in a small room close to the surgical suites), and he was right. I went back and was able to perform only a bypass to the very distal segment of the anterior descending branch. The patient died 48 hours later because the flow through the vein was unable to perfuse the entire left coronary distribution, highly compromised by proximal obstructions. The autopsy (I used to perform my own dissection) demonstrated, to my surprise, that the coronary arteries (left anterior descending and circumflex branches) were inside the muscle. The high price we paid was worthwhile. From then on we could solve the problem with an adequate operative approach. In the same presentation we emphasized for the first time the need for magnifying lenses to perform good distal anastomoses in small coronary arteries (we were applying them even in arteries of 1-mm diameter). The overall mortality rate, including all the combined procedures, was 5.4%. It is interesting to note that 50% of the patients received single or double mammary implants. It was hard for us to stop using Vineberg's technique because of our previous clinical experience with it. Careful reading of the cineangiogram helped us combine the direct and indirect approach. During the discussion after the presentation, surgeons were still concerned with the problem of late thrombosis, mainly with aneurysm dilatation. By June 1970,²⁸ 1,086 bypasses were performed with an overall mortality rate of 4.2% (see page 110 of reference 28).

I read our next presentation at the Fifth Annual Meeting of the American Association for Thoracic Surgery in Washington in April 1970.²⁹ It concerned the application of the coronary bypass technique to the left coronary artery and its divisions. We insisted upon the use of magnifying lenses and the "non-touch technique"—that is, no dissection of the coronary arteries was needed to perform the distal anastomosis: the pericardium was cut on top by a number 15 bistoury blade before the artery was opened. As a consequence, the stitches (we were using interrupted sutures) incorporated the epicardium and some of the subepicardial fat, a very important detail that surprised the hundreds of visitors at the Cleveland Clinic.

Once again, intramuscular coronary arteries were discussed. More distal anastomoses were performed and for the first time we demonstrated that even totally occluded vessels were reconnected. The use of cephalic or basilic arm veins as an alternative when the saphenous vein was not available was also discussed. Eleven cardiovascular centers contributed to the discussion and it was very pleasing to see the growth of coronary bypass surgery. There was a steady decrease in the number of combined single and double internal mammary implantations as a direct consequence of the growth of multiple bypass surgery. By August 1970,²⁹ 196 patients had undergone double, triple and quadruple grafts, with a 4.1% hospital mortality rate (see page 482 of reference 29).

After Sawyer et al's contribution,³⁰ we performed in 1970 some endarterectomies with the use of carbon dioxide, mainly in the right coronary artery, to find that, with the simple mechanical method used before, we obtained similar results, as was reported by Groves et al.³¹

In the same year, as a consequence of the superb work developed by New York's Green et al,³² I started using the direct mammary coronary anastomosis. I talked to Green on several occasions and he told me that I would need over 100 hours in the laboratory to learn how to use the microscope (that is the way he did the anastomosis). I thought that this approach would never popularize mammary coronary anastomosis and decided to dissect the left mammary artery and connect it to the anterior descending artery with the routine interrupted suture technique, with only the help of the lenses that we used in our daily work. I enlarged the indication to the diagonal and circumflex branches. After I left the Cleveland Clinic in 1971, Loop et al³³ emphasized and standardized this method and demonstrated the excellent results on long-term follow-up.³⁴

My book, "Surgical Treatment of Coronary Arteriosclerosis,"¹⁴ which was highlighted by Effler's introduction, appeared that same year. I analyzed all the experience gained at the Cleveland Clinic. The chapters on the anatomy of the coronary arteries and the interpretation of the different projections of the cine coronary angiogram were very helpful, mainly to our surgical colleagues, as testified to by the comments and the innumerable letters I received.

Finally, the VI World Congress of Cardiology was held at the Royal Festival Hall and Queen Elizabeth Hall in London during 1970. I was invited to participate in a symposium dedicated to coronary artery surgery with Drs. Ray Heimbecker, Arthur Vineberg and Charles Friedberg. The organizing committee gave us one of the smallest rooms. Cardiac adrenergic mechanisms were discussed at the same time in the main auditorium. I felt from the very beginning of the Congress the tremendous interest our session had aroused among the participants, a fact which was confirmed when I arrived an hour early to organize all my slides. The room was already packed by hundreds of doctors, occupying all the seats, some sitting in the central aisle on the floor, and others standing against the lateral walls. When we were on the podium, ready to start, the doors were closed, and I saw Paul Dudley White standing just in front of us. I thought: "How come that nobody leaves a seat to him, such an outstanding and humanistic physician who, together with Ignacio Chavez from Mexico, was the first to set the foundations of cardiology early in the forties?"

The first speaker, Dr. Heimbecker, started his presentation, and at the same time we could clearly hear the loud voices of the doctors who were complaining because they had been unable to enter the auditorium. The lateral doors finally crushed because of the pressure from outside and innumerable physicians jumped into the room. Somebody was able to protect the fragile body of Paul Dudley White. It was impossible to go on with the session. The Secretary of the Congress talked

to us and finally told the audience that we would repeat the symposium at 6 o'clock. We knew in advance that it would be impossible, because a discussion cannot be repeated and anyway Friedberg was traveling back to America that same evening. However, the Secretary's words calmed the audience down and the roundtable recommenced. Dr. Heimbecker presented his work on resection of acute myocardial infarction, Vineberg summarized his experience, and finally Friedberg and I discussed coronary artery bypass graft surgery. Charlie was an outstanding speaker who knew how to sprinkle his statements with good humor. He started by saying: "These cardiac surgeons are unique. When the heart has a hole they close it, when the heart doesn't have a hole they open one." We all laughed at his comments, but when I presented the number of procedures performed at the Cleveland Clinic and the perioperative mortality rate, Charlie voiced some doubts about "such a low mortality," which was difficult for him to accept. I flared up and invited anybody who wished to go to the Cleveland Clinic to check our files. In fact, some physicians did visit us on their way back to their native countries and were able to confirm the honest work performed at our institution.

At the same time Donald Ross invited me to perform some operations at the National Heart Hospital in London. I agreed and the first coronary bypasses were performed in England with his help. Some of the outstanding cardiovascular surgeons from Europe watched the surgeries from behind us, almost on top of our shoulders. I have to confess that I felt a tremendous responsibility and still remember the first operation, when, after opening the right coronary artery and placing the first stitch, which I had left on the operative field, the sister (a scrub nurse) pulled it off and tore the vessel. I prolonged the incision further distally and was able to solve the problem. Of course, I told the sister: "Please, don't touch anything else on the operative field." During that week, at noon, we went to a pub opposite the hospital, where we exchanged knowledge and friendship.

MY RETURN HOME

During my stay at the Cleveland Clinic I went back to my home country for short periods of time. I participated in national cardiology meetings and also performed some operations in 2 hospitals in Buenos Aires. A large delegation from Argentina attended the World Congress in London and, once more, many colleagues asked me to return home. From then on I gave serious thought to this matter and finally considered that my work and my duties in the United States were no longer needed. We had trained many capable fellows who would be able to continue the job. And a tremendous challenge stood in front of me, in the south.

In October 1970, late in the afternoon, I sat down and wrote my letter of resignation to Effler. It was a very difficult moment for me because I loved the place where I was working and the family that we had built up in the Cardiology and Cardiovascular Department. I

closed the envelope with tears in my eyes and left it on Effler's desk. I went home. I confess that I could not control myself and cried while driving through the beautiful roads that took me to Pepper Pike, where I had lived since 1966. Effler wrote back accepting my decision, "because I know that your roots have always been in Argentina." We had a long talk a few days later. I told him I had great faith in Loop and Cheanvechai, two outstanding fellows in our Department, and promised him that I would dedicate the rest of my time at the Cleveland Clinic to polishing them from the other side of the table. They performed most of my operations with dexterity and completed a successful training.

My big problem was Mason. It was impossible for him to accept that I would break our common work and brotherhood. Repeatedly he tried to convince me of my "mistake." The last 3 months were dreadful. Even though I may look like a strong and commanding surgeon, deep in my soul I am an extremely sensitive fellow. Everywhere I went in the Clinic, staff members of different departments, the nurses, the technicians, everybody, interrupted my work and asked me to stay. Finally I decided to escape. I told everybody I was leaving at the end of June or the beginning of July but accepted an invitation to lecture in Boston in the middle of June and from that meeting we went straight to Argentina. Only my secretary, Candice, a lovely young lady, knew my secret, and she was brave enough to keep it. I wrote letters to Effler and Sones. Donald accepted my decision, which "avoided a painful good-bye or farewell." Mason, once again, thought I was crazy.

I left an important part of my life at the Cleveland Clinic. I only know I worked hard in a friendly and clean atmosphere. But my departure was not a farewell. Since then I go back as frequently as I can. When the plane is landing in Cleveland I know I am back home. The most important trip was 4 weeks before Mason died. I had learnt through a telephone conversation with his secretary that he was in very bad shape, talked to Maria, and decided we would go and spend a weekend with him. It was a very difficult decision to make. I do not know where I got so much strength from. On Friday and Saturday we reminisced together, recalling anecdotes from our common work, mainly a long trip to Europe with our wives. During 3 weeks we had given lectures at different hospitals in France, Italy and Spain. On that occasion we went by car (I had rented a station wagon) from Marseille to Verona and I think Mason was in direct communication with nature for the first time. It was the end of summer. He was amazed by the wheat prairies, the corn fields, the green valleys, the vineyards and the fruit trees. We ate delicate homemade food and drank wine in small villages. This giant of modern cardiology was bathed by the sun in the middle of nowhere instead of by the lamps of the cardiac laboratory where he spent all his life.

These memories brought us happiness until Sunday, when we spent the last moments alone. Finally we embraced, cried together and said good-bye for the last time in this world. He died on August 29, 1985. I will

always thank God for having given me the opportunity to share with Mason many years of common work, understanding and deep friendship.

Final comments: I have summarized the contributions to myocardial revascularization performed at the Cleveland Clinic. I apologize for writing so often in the first person because I believe in team work and never claim any priority. Knowledge acquired in medicine is the result of the efforts of many contributors throughout the years. In coronary surgery it started in 1910 with the experimental work done by Alexis Carrel (see Table II of reference 1).

In 1971 I learned through direct communication from Effler of Garrett's first successful operation. In November 1964 he was trying to perform a patch repair of a localized obstruction on the anterior descending branch of the left coronary artery with the assistance of Drs. S. Pitzele, M.K. Neugebauer and L.C.C. Zanger, and he decided to perform a saphenous vein graft bypass because of some complications.

We suggested that he locate the patient, restudy him and publish the case, because if the vein was open, as it was, we would have the longer demonstration of a patent graft.³⁵ Nevertheless, I think I must honestly remark that, when the publication appeared in 1973, thousands of operations had already been done in Cleveland, in other centers in the United States, and even abroad.

Personally, I think the most gratifying aspect of my career refers to teaching: the deep rewarding feeling that comes from sharing what we have accumulated through many years of hard work, mainly with residents and fellows. This is the main reason why I came back to Argentina.

Some other time I hope to be able to write of what followed my departure from the Cleveland Clinic.

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Atrial Isomerism in the Heterotaxy Syndromes with Asplenia, or Polysplenia, or Normally Formed Spleen: An Erroneous Concept

Richard Van Praagh, MD, and Stella Van Praagh, MD

The concept of atrial isomerism¹⁻⁶ in the heterotaxy syndromes⁷ with asplenia, or polysplenia, or occasionally with a normally formed spleen is anatomically erroneous⁸:

First, a case with a morphologically right atrium bilaterally—that is, with bilateral inferior venae cavae, bilateral superior venae cavae, bilateral coronary sinus ostia, bilateral septa secunda, and bilateral pyramid-shaped appendages—has never been documented.

Second, a case with a morphologically left atrium bilaterally—that is, with four pulmonary veins bilaterally, septum primum bilaterally, and finger-like atrial appendages bilaterally—has likewise never been documented.

The concept of isomerism of the atrial appendages in the heterotaxy syndromes is also anatomically erroneous:

First, in studies of >100 postmortem cases of the heterotaxy syndromes,⁹⁻¹¹ we found that 1 appendage is often much larger and more anterior than the other. Because of differences in size and in anteroposterior location, the atrial appendages in the heterotaxy syndromes are not mirror-images, accurately speaking; that is, the appendages are not isomers.

Second, in addition to being anatomically erroneous (as aforementioned), the concept of atrial appendage isomerism is conceptually flawed. Partial isomerism—of the atrial appendages only, but not of the atria as a whole—is a contradiction in terms. Either isomerism applies to a whole structure—such as to a whole molecule or to a whole cardiac chamber—or it does not apply at all. D-glucose and L-glucose would not be isomers if only several hydroxyl groups were mirror-images. D-glucose and L-glucose are isomers because these molecules are complete (not partial) mirror-images of each other. Similarly, it would make no sense to talk about isomerism of the ventricular inflow tracts only, or of the ventricular outflow tracts only. Either the ventricles as a whole are isomers, or they are not. The same principle applies to the atria. Either isomerism applies to the atria as a whole (which it clearly does not, as was noted at the outset), or isomerism does not apply

to the atria at all—because partial mirror-imaging does not equal isomerism.

Consequently, the concept of isomerism of the atrial appendages is considered to be erroneous both anatomically and conceptually. This realization is important because it opens the way to the possibility of diagnosing the atrial situs in the heterotaxy syndromes. Conventionally, such cases have been considered to have atrial “*situs ambiguus*.” We now realize that this designation simply means that the atrial situs is undiagnosed.

Diagnosis of atrial situs in heterotaxy syndromes:

A review of 109 cases of the heterotaxy syndromes^{10,11} revealed that the atrial situs can be diagnosed in the majority of such cases, based on the following considerations.

It is generally accepted that the atrium into which the major horn of the sinus venosus (the right horn in situs solitus, the left horn in situs inversus) is incorporated is the morphologically right atrium.¹ The right horn of the sinus venosus includes the orifices of the inferior vena cava, the superior vena cava, and the smooth atrial wall between them. The coronary sinus, which represents the minor horn of the sinus venosus (the left horn in situs solitus, the right horn in situs inversus), normally opens into the sinus venosus component of the morphologically right atrium. Hence, the atrium that receives the inferior vena cava, the superior vena cava, and the ostium of the coronary sinus is the morphologically right atrium.

When the inferior vena cava is interrupted, its suprahepatic segment is always present. When this suprahepatic segment receives all the hepatic veins, it almost always connects with the morphologically right atrium. Occasionally, 1 of the hepatic veins may drain separately into the coronary sinus. If the coronary sinus is unroofed (absence of the coronary sinus septum), this separate hepatic vein may appear to drain directly into the left atrium. In this situation, other criteria, such as the connections of the pulmonary veins or the sizes and positions of the atrial appendages, may help to identify the morphologically right atrium.

We also found⁹⁻¹¹ that some or all of the pulmonary veins may drain into the right atrium because of malposition of the septum primum. We found that the pulmonary veins were connected normally, but that the septum primum was located abnormally. Hence, when all of the systemic veins and some or all of the pulmonary veins drain into 1 atrium—which is not a common atri-

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um because another small atrium is present—this large atrium contains the morphologically right atrium.

Until recently, we thought that an uninterrupted inferior vena cava always connected directly with the morphologically right atrium and hence could be used as a marker for the diagnosis of atrial situs.⁹ Now, however, we are aware of a case in which a noninterrupted, left-sided, small inferior vena cava connected with a normally roofed coronary sinus, and drained through this coronary sinus into a right-sided morphologically right atrium.¹⁰ This inferior vena cava received only 1 hepatic vein. All of the other hepatic veins formed a larger venous confluence that connected directly with the right atrium. This case made us realize that it is possible for the inferior vena cava to connect with the coronary sinus and then to drain into the morphologically left atrium through an unroofed coronary sinus, leading to an erroneous diagnosis of the atrial situs. In such cases, the sizes and positions of the atrial appendages and the connections of the pulmonary veins help to determine the correct atrial situs.^{10,11}

The morphologically right atrium was considered to be the atrium that received: (1) all of the systemic veins, while a separate atrium received all of the pulmonary veins; or (2) all of the systemic veins and some or all of the pulmonary veins, without being a common atrium because a second atrium is present; or (3) the orifice of a normal coronary sinus. Additional criteria for the identification of the morphologically right atrium, based on these studies,⁹⁻¹¹ concern the size and anteroposterior location of the appendages: the morphologically right atrial appendage usually is larger and more anterior than the morphologically left atrial appendage.

The morphologically left atrium was the atrium that received: (1) all or half of the pulmonary veins and none of the systemic veins—except for a persistent superior vena cava associated with an unroofed coronary sinus in cases with bilateral superior venae cavae; or (2) none of the pulmonary veins and none of the systemic veins. Additional criteria for the identification of the morphologically left atrium, based on the findings in these studies,⁹⁻¹¹ were that the left atrial appendage usually is smaller and more posterior than the right atrial appendage.

Success rates in the diagnosis of atrial situs: With the aforementioned venous criteria (1 to 3 for the right atrium, 1 and 2 for the left atrium), it was possible to diagnose the atrial situs in^{10,11}: (1) all 46 postmortem cases of the polysplenia syndrome (100%); (2) 21 of the 58 postmortem cases of the asplenia syndrome (36%); and (3) 1 of the 5 postmortem cases of the heterotaxy syndrome with a single, right-sided spleen (20%).

When the appendage criteria (size and anteroposterior position) were also taken into consideration, then it was possible to diagnose the atrial situs in: (1) 47 of the 58 cases of asplenia (81%); and (2) all of the single right-sided spleen cases (100%).

In the remaining 11 cases of the asplenia syndrome, the inferior vena cava, and the larger and more anterior atrial appendage, were contralateral. In these patients,

we could not be certain which criterion (venous or appendage) was more reliable concerning the diagnosis of the atrial situs; hence, we made the diagnosis of atrial situs ambiguous in these cases.¹¹

Success rates in the diagnosis of the types of atrial situs in living patients with the heterotaxy syndromes may not be as high, at least initially, as is now possible in postmortem cases. Current methods of echocardiography do not always permit accurate evaluation of the size, shape and position of the atrial appendages.¹¹ It is hoped that other methods, such as magnetic resonance imaging, may facilitate more precise evaluation of the atrial appendages, thereby increasing diagnostic accuracy in living patients.

Why are the atrial appendages similar in the heterotaxy syndromes? If the atrial appendages are not isomers, why then are they so similar: both rightish with asplenia, and both leftish with polysplenia?¹⁻³ The type of similar atrial appendages (rightish or leftish) is so consistent that it usually indicates with accuracy the type of heterotaxy syndrome that is present (asplenia or polysplenia, respectively). We hypothesize¹² that the shapes of the atrial appendages are related to hemodynamics in utero. The atrial appendages both are derived from the primitive atrium and at horizon 17 (34 to 36 days of age), both atrial appendages have a very similar shape¹⁰; both look quite "right." However, by horizon 22 (44 to 46 days of age), the characteristic differences in the shapes of the atrial appendages have normally begun to appear.¹⁰ Therefore the question is: why do the atrial appendages normally acquire such distinctive and different shapes¹³ from about 6 weeks of age onward?

In the normal heart,¹³ the inferior vena caval blood stream enters the right atrium from below and flows into the right atrial appendage, distending it. The superior vena caval blood stream flows down behind the right atrial appendage and through the tricuspid valve, not distending the right atrial appendage. Part of the inferior vena caval blood stream passes through the foramen ovale into the left atrium and flows behind the left atrial appendage through the mitral valve, not distending the left atrial appendage. Normally, therefore, the right atrial appendage is distended (triangular and relatively large), whereas the left atrial appendage is undistended (finger-like and relatively small).¹³

In the asplenia syndrome,^{14,15} the inferior vena cava is not interrupted and may enter the atrial part of the heart either to the right or to the left. Often there are 1 or more large contralateral hepatic veins (entering on the side opposite to that of the inferior vena cava). The atrial septum is very defective in association with common atrioventricular canal. Consequently, the entering venous blood streams coming from below can flow into both atrial appendages, distending both. Hence, in the asplenia syndrome, both atrial appendages are distended and consequently both appear rightish.

In the polysplenia syndrome,^{2,5} the inferior vena cava is typically interrupted. Thus, the systemic venous return from below is reduced to that of the hepatic veins. Hence, the atrial appendage opposite the hepatic

venous confluence (the suprahepatic segment of the inferior vena cava) is not as dilated as it normally is. The inferior vena caval stream returns through an enlarged azygos vein to a superior vena cava and then flows downward through the atrial cavity behind the atrial appendage(s) and through the atrioventricular valve(s) into the ventricular part of the heart—not distending either atrial appendage. Consequently, in the polysplenia syndrome, both atrial appendages are relatively undistended and hence appear leftish.

Thus, it is readily possible to understand the similar appearance of the atrial appendages in the heterotaxy syndromes on a hemodynamic basis,¹² rather than invoking the concept of isomerism. The definition of isomerism (mirror imagery) is right-left reversal, without anteroposterior or superior-inferior change. As noted heretofore, isomerism cannot explain the anatomic findings related to the atrial appendages in the heterotaxy syndromes because of the marked variations in the sizes of the right- and left-sided appendages, and because of the variations in the anteroposterior positions of these appendages, both of which do not conform to the definition of isomerism. Just as each patient has only 1 morphologically right ventricle and 1 morphologically left ventricle, so too each patient has only 1 morphologically right atrium with only 1 morphologically right atrial appendage, and only 1 morphologically left atrium with only 1 morphologically left atrial appendage.

Why does isomerism not apply to the heart? The heart is organized initially as a cephalocaudally oriented blood vessel. Right-leftness is only acquired later, during the course of normal development, but is not present de novo in the embryo. By contrast, in other viscera, such as the lungs, right-left organization is present de novo, and isomerism appears to apply accurately to such organs.

State of the spleen should not be ignored: Because of its clinical importance, the state of the spleen should not be ignored in diagnostic terminology. This is particularly true in the asplenia syndrome, in view of the ne-

cessity of life-long antibiotic prophylaxis in such patients.¹⁶

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Statistical Significance of Veterans Administration Vasodilator Heart Failure Trial Results

Jay N. Cohn, MD

The statistical significance of the mortality reduction observed in the Veterans Administration Vasodilator Heart Failure Trial (V-HeFT) from hydralazine-isosorbide dinitrate treatment of heart failure¹ has been the subject of some controversy. Since this could impact on the mandate for vasodilator therapy of heart failure and on the design of subsequent trials, the issue deserves further consideration. The urgency of this reconsideration has been hastened by the August article regarding the Studies of Left Ventricular Dysfunction (SOLVD) protocol,² in which an unfortunate typographical error identified the *p* value for V-HeFT as 0.93 rather than 0.093.

V-HeFT had 3 treatment arms: placebo, hydralazine-nitrate or prazosin added to digoxin and diuretics. The study was designed to compare placebo with combined vasodilator regimens if the results with the 2 treatments were similar, or with the individual vasodilator regimens if they were not. A 2-tailed test of significance was chosen (although in retrospect a 1-tailed test would have been appropriate because we were not concerned with an adverse effect of vasodilators) and a log-rank mortality analysis was designated.

It became apparent early to the Data Monitoring Committee—which remained blinded to the treatment arms—that 1 group was faring better than the others, and therefore all analyses performed compared individual rather than combined treatment arms. Comparison of the overall placebo and hydralazine-isosorbide dinitrate survival curves at the end of the trial revealed a difference with a *p* value of 0.093 using the specified log-rank test. Using a generalized Wilcoxon test, which gives somewhat more weight to the early events, the *p* value was 0.046. Some slight adjustment upward of these *p* values would be appropriate because of 4 “looks” at the data before termination of the study, but the magnitude of the adjustment would not be substantial because the stopping rules for the study before termination were extremely stringent. Consideration also could be given to the 2 possible comparisons proposed—combined vasodilator groups versus placebo and hydralazine-nitrate versus placebo—which might also impact on the significance of the *p* value. On the other hand, of course, a 1-sided test would have halved the *p* value.

The 2-year mortality also was designated in advance as an end point for the study, because it was anticipated that a positive treatment effect might wane over time as high-risk patients, perhaps kept alive by the treatment, could contribute to a progressively higher late mortality in the treatment group. Furthermore, comparison of survival curves in modest-sized studies usually includes adjustment for baseline differences between the treatment groups of variables that are shown in the trial to be related to survival. This adjustment requires modeling of the data using a Cox life-table regression model, which closely fit the data in V-HeFT. This modeling of the data with adjustment for baseline differences revealed an overall mortality reduction from hydralazine-isosorbide dinitrate of 28% (95% confidence interval 3 to 46%) and a 2-year mortality reduction of 34% (95% confidence interval 4 to 54%, *p* = 0.028).³

It is appropriate to compare this somewhat “borderline” statistical significance in V-HeFT with the prominent (*p* < 0.01) statistical significance of the mortality reduction observed with enalapril treatment in the Co-operative North Scandinavian Enalapril Survival Study (CONSENSUS).⁴ V-HeFT and CONSENSUS exhibited a similar percent mortality reduction at 1 year (Figure 1). The statistical significance of CONSENSUS—which indicates not the magnitude of the effect but rather the confidence in the effect being real—is related to the high death rate in this very sick population with class IV heart failure. Another important statistical difference is that CONSENSUS chose 1-year mortality as an end point, whereas V-HeFT opted for a longer study design. Indeed, the *p* value for a favorable effect of hydralazine-isosorbide dinitrate after 1 year in V-HeFT was 0.031, a significantly positive effect if reduction of 1-year mortality had been a prestudy goal.

The mortality reduction achieved with propranolol therapy in a postmyocardial infarction population in the Beta Blocker Heart Attack Trial (BHAT) is shown in Figure 1.⁵ The percent mortality reduction is similar to that in V-HeFT and CONSENSUS, but the efficiency of the treatment (i.e., the number of patients saved for every 100 treated as reflected by the absolute difference in height of the placebo and active treatment bars) is very low in the BHAT and remarkably high in the heart failure trials. Clearly it requires many more patients to demonstrate with some confidence a favorable effect of a treatment in a low-risk population.

The importance of the statistical power generated by such very large studies is dependent on the treatment one is studying and the implications one wants to draw

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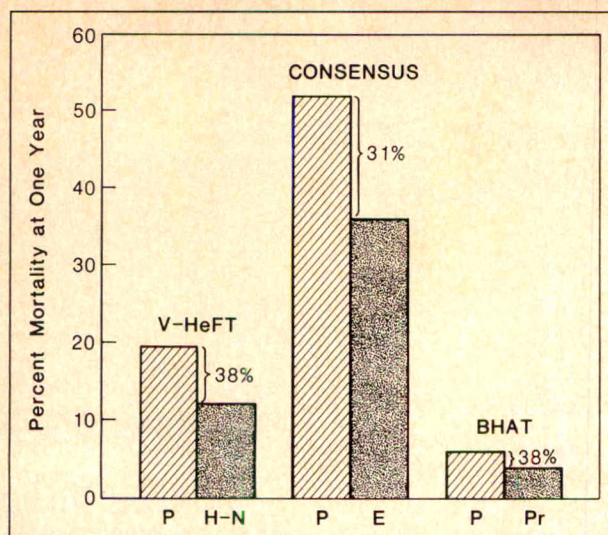


FIGURE 1. Comparison of 1-year mortality in the Veterans Administration Vasodilator Heart Failure Trial (V-HeFT), Co-operative North Scandinavian Enalapril Study (CONSENSUS) and Beta Blocker Heart Attack Trial (BHAT). E = enalapril; H-N = hydralazine and isosorbide dinitrate; P = placebo; Pr = propranolol.

from the study. If patient care is the concern, then mortality effects of a treatment must be considered in concert with its other actions. If the treatment is likely to exert an adverse effect on some aspect of quality of life—as propranolol may have in some postmyocardial infarction patients—then great confidence in the mortality reduction should be required and identification of the subset at greatest risk should be attempted before the treatment is administered. If, however, the therapy is relatively inexpensive and safe and known to affect favorably some manifestations of the disease—as is true with hydralazine-isosorbide treatment of heart failure—then a favorable trend in mortality may be all that is needed to decide that the therapy should be included in the management of the disease. It thus seems immaterial in V-HeFT if the chance is 1 in 10 or 1 in 20 that the mortality difference has occurred by chance. Certainly, the likelihood is far greater that the vasodilator regimen *did* prolong life and that the therapy therefore should be administered to, rather than withheld from, patients with heart failure.

On the other hand, if the issue is a regulatory decision to approve a treatment for mortality reduction or it

is the ethics of embarking on another placebo-controlled trial, there is room for disagreement. Scientific discipline has promulgated insistence on a chance occurrence of <1 in 20 times to establish firmly a therapeutic principle. To the extent that statistical disciplinarians may be unwilling to accept the borderline significance of V-HeFT as proof of efficacy on survival, other trials may be initiated. SOLVD was undertaken to address the effect of enalapril on survival in patients with left ventricular dysfunction with or without symptoms of heart failure. But out of deference to the V-HeFT data, symptomatic patients were allowed to enter SOLVD while receiving vasodilators other than converting enzyme inhibitors.

These considerations remind all of us that the interpretation of large-scale clinical trials is at least as complicated as planning them and carrying them out. It is important to keep in mind that trials are conducted to improve the precision of our clinical management. The more complicated the disease process—and heart failure is certainly complex—the more therapeutic options there are and the more difficult it is to prove the benefit of any one. V-HeFT and CONSENSUS have provided critical new insights that bear on mechanisms as well as on mortality. SOLVD, V-HeFT II and other studies to come will hopefully add important new information that should further our goal to define the optimal therapeutic approach to heart failure.

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Transient Electrocardiographic Changes of Elective Coronary Angioplasty Compared with Evolutionary Changes of Subsequent Acute Myocardial Infarction Observed with Continuous Three-Lead Monitoring

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The current use of continuous multilead monitoring with high-resolution digital systems¹ during clinically unstable situations has greatly augmented the versatility of the electrocardiogram. A recent study² of patients undergoing elective percutaneous transluminal coronary angioplasty (PTCA) reported multilead patterns of peak ST-segment elevation and depression that were reproduced by later reocclusion of the same coronary site. In related work,^{3,4} detailed quantitative analyses of dynamic changes in the QRS complex and ST segment during PTCA-induced ischemia were presented in the most active lead of each patient. Occasionally an acute myocardial infarction (AMI) develops spontaneously in the hours after an elective PTCA. Use of continuous electrocardiographic monitoring would facilitate comparisons between the dynamic changes of the "controlled" ischemic period during the PTCA and the spontaneous ischemic period of the AMI by using each patient as his own baseline. Such information may provide a more complete understanding of the evolution of the acute ischemic process. Using continuous 3-lead monitoring in 4 carefully selected patients with elective PTCA who subsequently developed AMI, this study quantitates and compares dynamic characteristics of the ST segment occurring during both ischemic events.

The records of all patients with continuous 3-lead monitoring during elective 1-vessel PTCA and in the 24-hour period after the procedure at Georgetown University Hospital during 1984 to 1986 were reviewed (n = 512). Of these, 35 patients had documented enzymatic evidence of AMI during the monitoring session. These 35 records were examined in detail for inclusion in this study, which required: (1) a baseline standard 12-lead electrocardiogram obtained before PTCA with no ventricular hypertrophy, bundle branch block, fascicular block or paced rhythm; (2) no attempted reperfusion during the evolving AMI; (3) continuous monitoring of ≥ 2 electrocardiographic leads during the 24-hour period, inclusive of both the PTCA and the AMI, including the lead that would be expected to have the most ST-segment activity⁵; and (4) a stable standard 12-lead electrocardiogram after the monitoring session and before

hospital discharge. The final study group consisted of 4 patients: 1 with angiographic left anterior descending occlusion and 3 with right coronary occlusion.

Electrocardiographic monitoring was performed using a Scole Alta II 3-channel precalibrated Holter AM recorder. Before PTCA, radiolucent leads were positioned on the patients in the anteroposterior (V_2), left-to-right (V_3) and inferosuperior (aVF) configurations.⁶ Playback analysis was performed retrospectively on a digitizing Marquette 8000 Holter analysis system interfaced to a DEC PDP 11/34 minicomputer.

Based on prior studies,³⁻⁵ it had been demonstrated that the electrocardiographic lead that showed the most ST-segment activity during the monitoring session would be lead V_2 for patients with left anterior descending occlusion, and lead aVF for those with right coronary occlusion. Accordingly, only these "most active" leads were evaluated in detail for each occlusion site. Manual measurements of the ST segments were performed at the J point to the nearest 0.5 mm at sequential intervals, defined specifically later.

The balloon inflation that produced the greatest ST-segment deviation in the most active lead ("maximum PTCA ST") was identified for each patient, and its duration was noted. The duration of this period of controlled ischemia was not uniform for all patients because the lengths of the dilatations varied. The ST-segment deviation was measured at 10-second intervals throughout the duration of the balloon occlusion.

A high-resolution ST-segment trend of the most active lead during the entire monitoring session was computer-generated for each patient by plotting the mean ST level from every 15 seconds of acquired data over time. Combined with the clinical history and the electrocardiographic records, these trends were valuable in helping to detect onset and duration of the AMI for each patient. AMI "onset" was defined as the time after PTCA at which the trend recording revealed an ST-segment deviation of ≥ 0.5 mm in the most active lead, which persisted and successively worsened. Such changes may or may not have been accompanied by chest pain. AMI "duration" was defined as the interval from AMI onset to the time at which the ST-segment deviation was observed to have resolved to a steady state at or approaching the baseline level. Observations on the ST trends were always corroborated by manual review of the electrocardiographic records.

To discern whether the ST-segment changes of AMI occurred at the same rate and had a similar pattern as those induced by the controlled coronary occlusion of

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TABLE I Transient Versus Evolutionary ST Changes

Pt.	Coronary Artery	Maximum PTCA ST Δ		Acute Infarct			
		Inflation	Duration (sec)	Onset After PTCA		Duration	
				Hours	Minutes	Hours	Minutes
1	Right	2	55	16	11	1	31
2	Right	3	90	9	49	1	39
3	Right	1	59	9	53	4	8
4	LAD	2	98	18	43	1	38

LAD = left anterior descending; PTCA = percutaneous transluminal coronary angioplasty; ST Δ = ST-segment change.

PTCA, the records of the earliest seconds of the AMI onset that corresponded in time to the length of maximum PTCA ST segment were isolated for comparison. The AMI ST-segment deviation was quantified at 10-second intervals and matched to the measurements of maximum PTCA ST segment that had been performed previously (see above).

To determine the ischemic changes that evolved during the subsequent infarction process, ST-segment deviation was additionally measured at the initial 10-minute marker after AMI onset and at sequential 10-minute

intervals throughout the duration of the AMI. This analysis made it possible to depict the continuum of ST-segment change by using each patient as his own control.

The Selvester QRS scoring system⁷ was applied to the standard baseline electrocardiogram that had been taken before PTCA to determine the extent of infarction, if any, which existed before the procedure, and to the stable predischARGE electrocardiogram to determine the total amount of infarction. Any difference between the standard and the predischARGE sizes would be expected to reflect the amount of left ventricular AMI that had occurred in the left ventricle during the monitoring session.

Of the 4 patients who met the rigorous criteria for inclusion in this study, 3 received right (patients 1 to 3) and 1 left (patient 4) anterior descending coronary artery PTCA (Table I). The period of inflation that produced maximal PTCA ST-segment deviation had a mean duration of 75.5 seconds (range 55 to 98). The subsequent AMI onsets varied between 10 and 19 hours after the conclusion of PTCA, and the AMI durations ranged from 1.5 to 4 hours.

In 2 of the 3 patients with right occlusion, the electrocardiogram showed initial ST depression during PTCA, which was quickly replaced by elevation. In 1 of these patients, minor ST-segment depression was evident during the corresponding seconds of the AMI (Figure 1), and in the other there was only ST elevation during the AMI (Figure 3). In 2 of the 3 patients with right occlusion (Figures 2 and 3), both the pattern and extent of ST-segment elevation seen during PTCA was nearly identical to that observed during the same time sequence of the AMI. Although the 1 patient with left anterior descending occlusion (Figure 4) had ST elevation during both ischemic events, there was marked elevation during the PTCA but only minimal change during the corresponding seconds of the AMI.

The ischemic changes during the developing AMI process were compared among the patients. Only patient

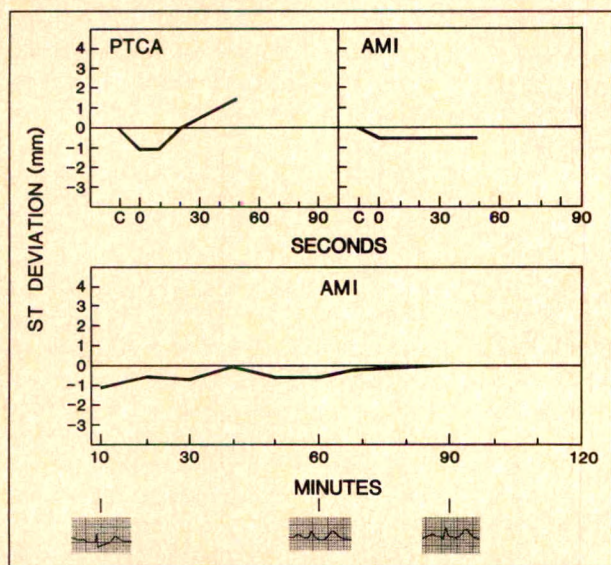


FIGURE 1. The dynamic changes of the ST segment during percutaneous transluminal coronary angioplasty (PTCA) and acute myocardial infarction (AMI) in a patient with right occlusion (lead aVF). *Top left*, the length of the inflation that produced "maximum PTCA ST" deviation in 10-second intervals from control (C), inflation (0) to 100 seconds. The *bold line* represents the magnitude of ST change throughout this inflation; *top right*, magnitude of ST change seen in the earliest discernible corresponding seconds of the AMI "onset" as measured in PTCA-matched 10-second intervals; *bottom* quantifies the ST change during the length of the AMI beginning at the initial 10-minute marker and continuing at sequential 10-minute intervals. The *bold line* depicts the dynamic ST-segment changes as the AMI evolves and eventually reaches a "steady state" at or approaching the baseline ST level. Electrocardiograms obtained from the continuous records at selected intervals illustrate the changes that occur with AMI. Lead aVF is shown.

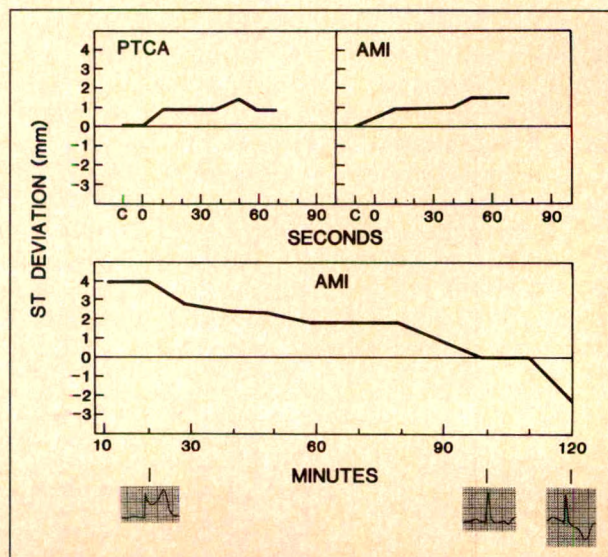


FIGURE 2. See description of Figure 1.

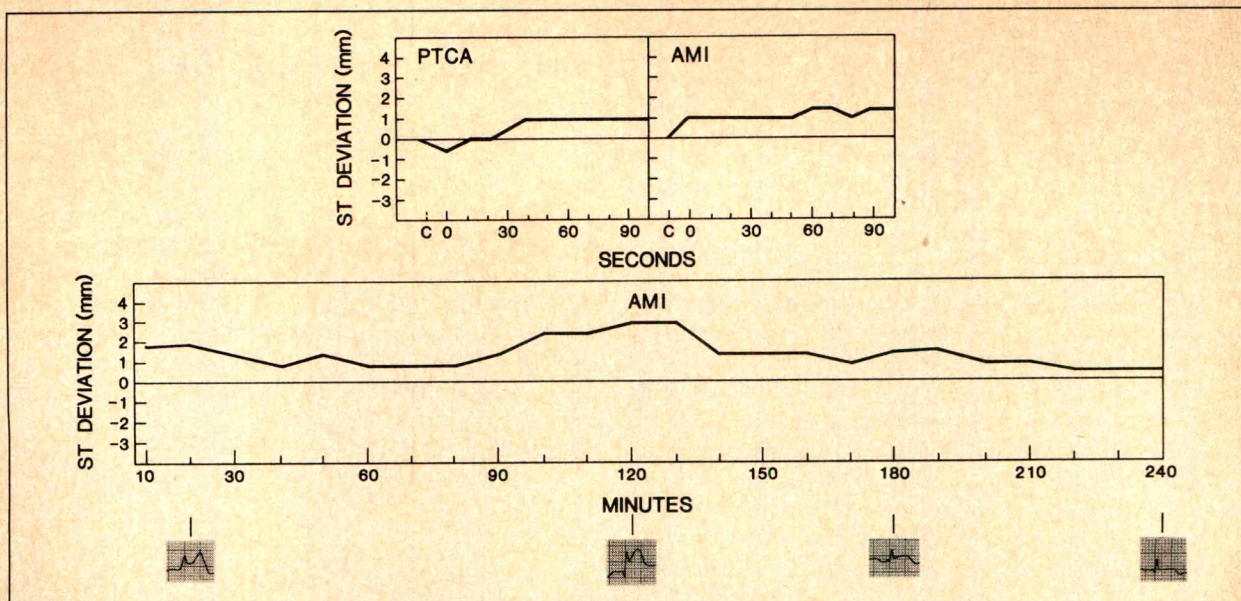


FIGURE 3. See description of Figure 1.

1 had ST-segment depression throughout the earliest seconds of the AMI, and this continued to an even greater extent in the following minutes. Patients 2 to 4 experienced ST-segment elevation in the initial seconds of their AMI, which successively increased and peaked in magnitude between 10 and 30 minutes after AMI onset. Patient 3 appeared to have an "extension" of the ischemic process, with a second peak of ST-segment elevation occurring late (100 to 130 minutes).

The 4 patients experienced varying amounts of QRS-estimated AMI during the monitoring session involving 0, 3, 12 and 15% of their left ventricles. The patient with only ST-segment depression developed no QRS evidence of AMI (Figure 1), whereas the patient whose electrocardiographic record suggested "extension" had the greatest amount of AMI (Figure 3).

The patients included in this study were culled from over 500 persons who were monitored continuously for 12,000 hours during both an elective PTCA and the successive 24 hours. Of the 35 patients with enzymatic evidence of AMI after the procedure, only 4 satisfied the other rigorous criteria required for inclusion in this study. These meticulously selected patients by chance demonstrated diverse ST-segment variability and, while not a statistical force, may help to direct future investigations. A significant weakness of this study is the inability to determine whether the AMI that occurs within hours of a PTCA is representative of an AMI that occurs "naturally." A great advantage of this study is the ability to compare the transient ST changes due to PTCA with those during the corresponding initial seconds of the subsequent AMI using each patient as his own control.

Krucoff et al² observed a change in direction of the ST-segment deviation during elective PTCA in approximately 15% of patients. This has been corroborated by other investigators who found that the degree of retrograde flow from collaterals affects both the extent⁸ and the direction⁹ of ST-segment deviation. The dynamic na-

ture of collateral support has also been described.¹⁰ In the present study, collateral flow may explain the transient initial ST depression seen during PTCA in patient 1 (Figure 1) and during the subsequent AMI. This is perhaps due to a pathophysiologic process such as an intimal flap, coronary spasm, or platelet/thrombus formation causing only subtotally occluded anterograde flow. Either persistent collateral support, or a "trickle" of anterograde flow, may have prevented the ST elevation of epicardial injury.

The transient total occlusion of a vessel during PTCA is often observed to produce a rapid increase in the ST segments because of a total absence of local coronary flow. A spontaneous AMI, which was initiated by abrupt

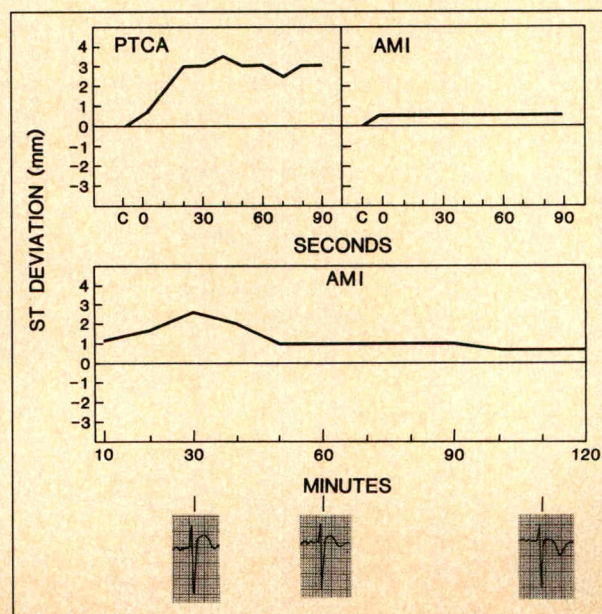


FIGURE 4. See description of Figure 1, except lead V₂ is shown for this patient with left anterior descending occlusion.

occlusion of a vessel, also would likely show a similar initial increase in the ST segments. As the AMI evolved, sustained closure of the vessel would show either a prolonged period of "plateau" ST elevation or a period of gradually increasing ST-segment change. Such ST-segment activity was observed in patient 2. The persistence of the occlusion beyond 60 seconds during the AMI eventually caused a doubling of the extent of the ST elevation that occurred during PTCA (Figure 2).

A plateau followed by a second peak of ST elevation has been associated with recurrent creatine kinase-MB increase,¹¹ thus suggesting AMI extension. The initial peak of ST-segment elevation seen in patient 3 (Figure 3) is followed by an interval of sudden but partial ST recovery, and then a second ST peak and recovery period, representing early AMI extension. Monitoring of ischemia may lead to redefinition of AMI extension, previously thought to occur only after the first 24 hours when both electrocardiographic and enzymatic indexes had stabilized.

It might be expected that both magnitude and time course of ST-segment elevation during PTCA would be the same as that which occurs during the corresponding initial seconds of a spontaneously occurring AMI. Indeed, in 2 patients in the present study, such changes were nearly identical (Figures 2 and 3). However, for patient 4, the ST magnitude during the first seconds of the AMI was markedly less than that observed during the PTCA. It was not until 30 minutes into the infarction process (Figure 4) that maximum ST elevation of PTCA was attained. Clearly observable in this patient was the ST "fingerprint" pattern² of the PTCA, which was repeated during the 10- to 30-minute period of the AMI.

In the 3 patients in the present study with ST-segment elevation early during AMI (Figures 2 to 4), the maximal change was attained between 10 and 30 minutes. This peak was then followed by a rapid decline to a plateau similar to that observed in other studies.^{11,12} These data suggest that the peak of ST activity either occurs much earlier than has been commonly accepted, or that an AMI that occurs within hours after PTCA is not representative of a truly spontaneous event. Similarly, it was surprising that 3 of 4 patients "completed" AMI within approximately 90 minutes after its onset (Table I), attributable perhaps to the relatively small sizes of these AMIs (0 to 12%). The single patient (Figure 3) who had the typical longer time course of 4 hours also experienced probable AMI extension of the largest size (15%).

Even this small series of patients demonstrates that there are a variety of sequential electrocardiographic

manifestations of AMI, most of which mimic the changes occurring during PTCA. These range from ST-segment depression, to ST elevation that requires a prolonged period of time to reach the level achieved almost immediately during PTCA, to ST elevation that quickly attains the level observed during PTCA and then either resolves or progresses to higher levels. These nonuniform patterns of change suggest the presence of pathophysiologic processes that are different from the ideal model of the sudden complete occlusion of PTCA. Widespread use of continuous, multilead electrocardiographic monitoring, together with the growing population of patients undergoing therapy, provides the potential for further documentation of the electrocardiographic manifestations of AMI in humans.

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Long-Term Clinical and Angiographic Follow-Up of Percutaneous Transluminal Coronary Angioplasty in Patients ≥ 65 Years of Age

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The expansion of percutaneous transluminal coronary angioplasty (PTCA) indications affects different subsets of patients including elderly patients (age ≥ 65 years).¹ PTCA provides an attractive revascularization technique compared with coronary bypass surgery, particularly in elderly patients.²⁻⁴ The initial outcome of PTCA in this population is well established,^{2,3} and the clinical follow-up of elderly people subjected to PTCA has been reported recently.⁴ Nevertheless, no systematic information exists regarding the angiographic changes and, in particular, the restenosis rate of PTCA performed in elderly people. This report evaluates the clinical long-term results and especially the angiographic follow-up of PTCA in patients aged ≥ 65 years.

From March 1985 to July 1988, 145 consecutive patients aged ≥ 65 years underwent PTCA at our institution. They represented the 29% of our total PTCA population during that period. The remaining 355 patients < 65 years who had dilatation were used as a control group. Elderly patients underwent 183 PTCAs (38 [20%] as repeat procedures) in the treatment of 223 lesions. Patients < 65 years had 414 PTCAs (59 [14%] as repeat procedures) in an attempt to dilate 484 lesions. Different clinical, angiographic and procedural variables were prospectively entered into a computer database when PTCA was completed. Unstable angina was defined according to the National, Heart, Lung, and Blood Institute PTCA Registry criteria.⁵ Only lesions with $\geq 75\%$ of luminal narrowing were considered for dilatation. Lesion morphology was independently determined by 2 experienced observers who subsequently reached a consensus in case of disagreement. Primary angiographic success was defined as a residual stenosis $< 50\%$ of luminal narrowing and PTCA success as angiographic success at least in the culprit lesion in the absence of any major complication. Clinical follow-up information was obtained in an outpatient clinic specifically created with this aim during visits at 0.5, 3, 6 to 9 months and every year thereafter. In every visit, symptomatic status and adherence to medication was assessed and an exercise test was performed. This information was also added to the database when obtained. To assess the angiographic long-term results after PTCA, we followed a prospective protocol that included a repeat coronary angiogram at 6 to 9 months, even for asymptomatic patients unless clinical indications suggested it to be done early. Restenosis was defined when ≥ 1 of the lesions had a recurrence in luminal narrowing $\geq 50\%$. Sta-

tistical analysis was performed with Student's *t* test and the chi-square or Fisher's exact test to compare continuous and categorical variables, respectively. A stepwise logistic regression analysis was used to determine if age ≥ 65 years was independently associated with a higher restenosis rate. A *p* value < 0.05 was considered significant.

Clinical baseline characteristics in the 2 groups are compared in Table I. The reason for PTCA was different in the 2 groups, and elderly patients had a higher incidence of angina but less frequently underwent PTCA after an acute myocardial infarction. PTCAs were performed at the time of initial cardiac catheterization in 28 and 29% (difference not significant) and as an emergency procedure in 11 and 10% of elderly and young patients, respectively. Ejection fraction was similar in both groups (62 ± 14 vs $63 \pm 13\%$), but elderly patients presented a higher incidence of multivessel disease (50 vs 33%, $p < 0.001$) and had lesions more frequently located in the left anterior descending coronary artery (59 vs 48%, $p < 0.05$). Lesion morphology in both groups is shown in Figure 1. A complete revascularization was achieved in a higher percentage of patients < 65 years (72 vs 56%, $p < 0.001$). PTCA success and major complications were similar in both groups and are listed in Table II. Of the 160 successful PTCAs in elderly patients, 142 (89%) had angiographic follow-up 7 ± 1 month after PTCA. Alternatively, of the 355 successful PTCAs in patients < 65 years, 326 (92%) had a control angiogram available 7 ± 2 months after PTCA. Restenosis rate was higher after PTCA in elderly patients (59 [42%] vs 97 [30%], $p < 0.05$), but age was not independently related to restenosis on multivariate analysis. However, other clinical variables, such as diabetes ($p < 0.005$) and unstable angina ($p = 0.05$), and anatomic variables, such as left

TABLE I Clinical Baseline Characteristics

	≥ 65 Years	< 65 Years	<i>p</i> Value
Patients	145	355	
Age (years)	71 ± 5	54 ± 8	< 0.005
Male/female	100/45	326/29	< 0.001
Systemic hypertension*	78 (54%)	135 (38%)	< 0.005
Cigarette smoking	77 (53%)	284 (80%)	< 0.001
Hypercholesterolemia†	56 (39%)	121 (34%)	NS
Diabetes mellitus	38 (26%)	50 (14%)	< 0.005
Previous myocardial infarction	59 (41%)	142 (40%)	NS
Unstable angina	91 (63%)	177 (50%)	< 0.001
Acute myocardial infarction‡	12 (8%)	76 (21%)	< 0.05

* Blood pressure $> 170/95$ mm Hg.

† Total cholesterol > 250 mg/dl.

‡ Patients with acute myocardial infarction are not included in the group with previous myocardial infarction.

NS = not significant.

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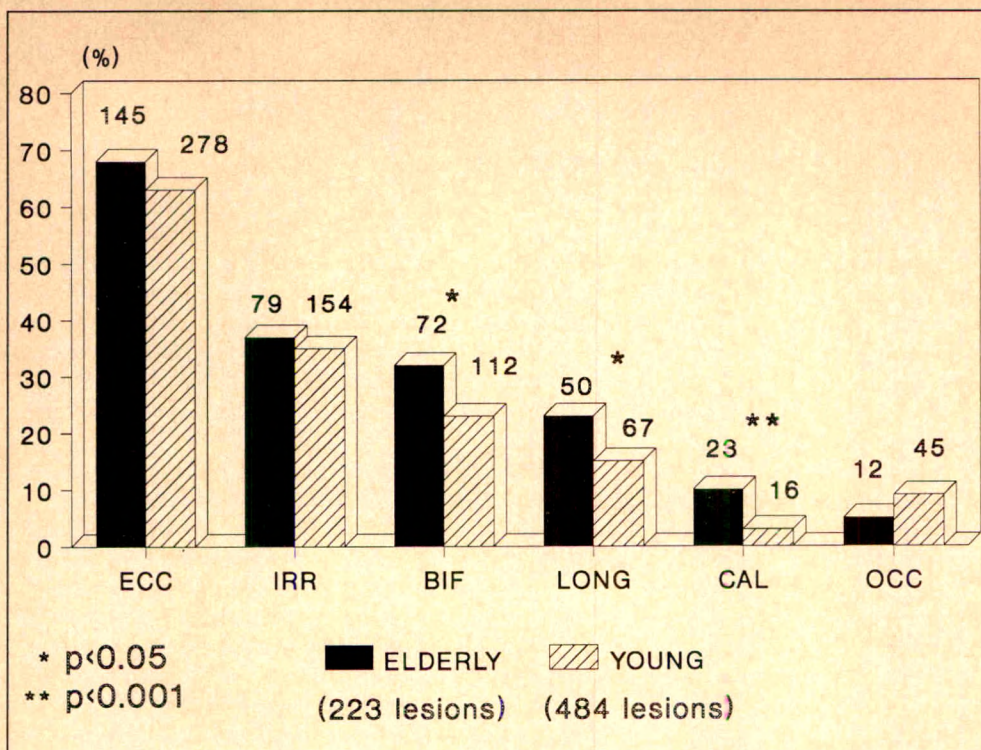


FIGURE 1. Lesion morphology. BIF = lesions located at bifurcation. LONG = long lesions (≥ 12 mm). CAL = calcified lesions; ECC = eccentric lesions; IRR = irregular lesions; OCC = lesions with total occlusions.

anterior descending coronary artery location ($p < 0.05$) and lesion length ($p < 0.05$), were independently associated with restenosis. Clinical follow-up in elderly patients was 27 ± 11 months. During this time 4 (3%) patients died, 6 (4%) underwent coronary artery bypass surgery and 42 required repeat PTCA. When the repeat PTCA was considered as an integral part of the PTCA strategy and was not considered an untoward event, at last clinical follow-up 113 patients (78%) with successful dilatation eventually remained asymptomatic and event free.

Previous reports have demonstrated the safety and effectiveness of PTCA in elderly people with results similar to those obtained in younger patients.^{2,3} The increased morbidity and mortality of surgery in this age group has lead to the widespread use of PTCA as an attractive alternative in elderly patients even in the presence of multivessel disease.¹ Recently, Simpfordorfer et al⁴ reported that the long-term clinical follow-up is also favorable in patients ≥ 70 years old. In that study, when repeat

PTCA was excluded as an event, $>70\%$ of patients who underwent PTCA for stable or unstable angina survived ≥ 4 years without myocardial infarction or the need for bypass surgery. Our study confirms not only that PTCA provides a favorable early outcome, but also that if repeat PTCA is considered as an integral part of the PTCA strategy, most elderly patients (78%) remain asymptomatic in the follow-up. In addition, our study provides new information concerning the angiographic follow-up of these patients. With a high angiographic follow-up available, our results suggest that restenosis in this age group is higher than that found in younger patients. However, our elderly population presented a higher incidence of both clinical and angiographic factors (including unstable angina, diabetes, multivessel disease, left anterior descending coronary artery location and long lesions) that increase the likelihood of developing restenosis.⁶ In fact, when these variables were taken into account the restenosis rate for elderly and young patients was similar. These results emphasize the importance of accurately stratifying elderly candidates for PTCA according to baseline clinical and angiographic characteristics, so that patients at higher risk of restenosis, who will require a closer follow-up, will be readily identified.

TABLE II Results and Complications After PTCA

	≥ 65 Years	< 65 Years	p Value
Primary angiographic success	197/223 (88%)	434/484 (89%)	NS
PTCA success	160/183 (87%)	355/414 (86%)	NS
AMI	5 (2.8%)	14 (3.4%)	NS
Emergency CABG	0 (0%)	2 (0.6%)	NS
Death*	2 (1%)	3 (0.8%)	NS

* Total mortality during hospital admission for PTCA (including noncardiac deaths). AMI = acute myocardial infarction related to PTCA; CABG = coronary artery bypass grafting; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

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Insurance Reimbursement for Preventive Cardiology Services

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In recent years, there has been an increase in programs that teach children and families healthier lifestyle habits. These emphasize nutrition and exercise to prevent the onset of coronary artery disease. However, although 2 studies have examined life insurance eligibility of children with congenital cardiovascular disease,^{1,2} no study as yet examines whether insurance companies will provide reimbursement to families for evaluation and treatment of risk factors for coronary artery disease. Typically, many insurance companies do not provide for well child-care or for nutrition counseling, though these services have definite health benefits. This may deter physicians from recommending preventive programs for their patients and may deter families from seeking preventive care. This study determines the degree to which insurance companies reimbursed families for an initial evaluation for cardiovascular risk and for a 1-year intervention program. We also asked whether children with familial hypercholesterolemia would be more likely to receive insurance reimbursement than would families with other types of hyperlipidemia.

The investigators contacted all 101 families who had initial intake evaluations (Table I) in the Preventive Cardiology Program from October 1987 through February 1989, including 40 families who enrolled in a 6-month small-group intervention program (Table I). Each of these families had ≥ 1 child suspected to be at high risk for the development of coronary artery disease. Families were asked whether they applied for health insurance, whether they had met their deductible and how much the insurance company reimbursed them for both intake and intervention. The families' reported levels of reimbursement were verified against hospital billing records.

When families received no insurance coverage, they were categorized according to whether the insurance company refused reimbursement, whether they had actually applied for insurance or whether they had met their deductible. Reimbursed patients were also categorized according to the level of reimbursement. Fisher's

exact test and frequency distributions were used to further analyze the data set.

Phone contacts and verification of hospital billing records were available for 72 (71%) of the 101 intake families and for 34 (85%) of the 40 families who subsequently enrolled in the intervention program. Diagnoses of the 72 intake patients included familial hypercholesterolemia in 14, other lipid abnormalities in 53, and normal lipids with other risk factors in 5. Of the 72 intake families contacted, 45 (63%) received some insurance coverage. Of those covered, 41 received 50 to 100% reimbursement. Medicaid provided payment for 6 (8%). Insurance companies denied reimbursement for the intake program to 16 (22%). The 5 families who paid for the intake program did so either because they did not apply for reimbursement ($n = 4$) or had not met their deductible ($n = 1$) (Table II).

Insurance companies were also willing to reimburse for the intervention program provided by a dietician, health educator and psychologist. Of the 34 families, 23 (67%) received some insurance reimbursement. Of those 23 families who received reimbursement, 19 received 50 to 100% reimbursement. An additional 2 (6%) were covered by Medicaid, and 2 (6%) paid for the intervention program, not having applied for insurance reimbursement. Insurance reimbursement was denied to 7 (21%) of the 34 intervention families (Table II).

TABLE I Intake and Intervention

Initial Evaluation for Cardiovascular Risk (Intake)
Physician consultation ($\frac{1}{2}$ hour)
Nutrition evaluation (1 hour by RD)
Behavior modification ($\frac{1}{2}$ hour by MPH or PhD)
Lipid studies, biochemical and anthropometric measurements of growth and nutrition
Cost: \$195.000
One-Year Program to Lower Cardiovascular Risk (Intervention)
4 small-group sessions (2 hours, each led by RD and MPH)
1 behavior modification small-group session ($1\frac{1}{2}$ hours led by PhD)
4 nutrition consults with individual family ($\frac{1}{2}$ –1 hour led by RD)
1 behavior modification consultation with individual family (1 hour with PhD)
Cost: \$500.00
All costs cover the evaluation and treatment of up to 4 people, 2 parents and 2 children. MPH = health educator; PhD = psychologist; RD = dietician.

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TABLE II Insurance Reimbursement

	Intake	Intervention
No. of families	72	34
Insurance-reimbursed families (%)	45 (63)	23 (67)
100% (includes HMO)	13 (18)	3 (9)
>50%	28 (39)	16 (47)
≤50%	4 (6)	4 (12)
Medicaid (%)	6 (8)	2 (6)
Self-pay (%)	5 (7)	2 (6)
Had not met deductible	1 (1)	0 (0)
Did not apply for insurance	4 (6)	2 (6)
Insurance denied (%)	16 (22)	7 (21)

HMO = health maintenance organization.

There was a trend toward better reimbursement for intake patients with familial hypercholesterolemia than for other lipid abnormalities, with a greater proportion of families with familial hypercholesterolemia receiving reimbursement than for intake families without familial hypercholesterolemia (91 vs 69%, $p = 0.11$). This trend was not found for the intervention families.

There was great heterogeneity in level and type of insurance coverage for both intake and intervention families. Fifty-one intake families reported 18 different rates of insurance coverage ranging from 28 to 100%. The mode for coverage was 80%, with 19 (41%) receiving this level of coverage. Thirteen families (28%) received 100% coverage; about half ($n = 6$) were participants in a health maintenance organization. All health maintenance organization patients received full coverage. Only 1 patient's policy expressly based reimbursement on an abnormal cholesterol level. For the 22 intervention patients who received reimbursement, 10 different rates of coverage ranging from 30 to 100% were reported. The modal coverage was 80%, with 9 of 22 (41%) receiving this level of coverage. Only 3 of 22 (14%) received 100% coverage, and 2 of these were health maintenance organization participants. In addition to variation in the rate of coverage, there was a significant variation in the deductible.

This study shows that most patients seen at a tertiary center for evaluation and treatment of hyperlipidemia received some insurance coverage. Given that the current recommended treatment for most hyperlipidemic children is dietary therapy,^{3,4} it is heartening that most families received some reimbursement for a dietary approach to therapy.^{3,4} Nutrition education programs are essential for families with unsatisfactory diets, particularly when the parents themselves have previously untreated or unrecognized hyperlipidemia.⁵

Reimbursement may have been aided by individual staff letters to insurance companies recommending the intervention program for treatment of hyperlipidemia rather than for prevention of coronary artery disease for patients whose insurance companies initially denied reimbursement. The rate of reimbursement may have been improved by the hospital-based setting and billing under the umbrella of cardiology. Had the dietician and psychologist/health educator provided care in a private office or under their own disciplines, reimbursement for these same services may have been denied. Also, we do not know how many patients did not schedule intervention appointments because of a priori knowledge that insurance would not cover bills.

Type of insurance coverage for families was greatly diverse and lacked a consistent policy with regard to coverage of hyperlipidemia therapy. The ambiguous nature of current medical insurance leads to higher administrative costs for hospitals and stress for families caught between an insurance company whose policy is ambiguous and a hospital anxious for reimbursement.

New economic forces on the horizon may impact both positively and negatively on reimbursement for nutritional counselors and treatment of hyperlipidemia. Reimbursement policies vary from state to state, as well as from policy to policy. Value-related reimbursement scales presumably will place a higher value on the time-intensive counseling required for hyperlipidemia treatment.⁶ National guidelines for nutrition therapy will provide a solid background for treatment recommendations, particularly if they are focused on a select high-risk group. However, if guidelines identify a large percentage of the population as high-risk, reimbursement might be compromised by an unwillingness to support the large manpower cost of this effort. Finally, hyperlipidemia programs may be vulnerable to broad-based measures by third-party payers to cut health care costs on a national scale.

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Prognostic Value of Junctional Recovery Times and Long-Time Follow-Up of Complete Atrioventricular Nodal Block at a Young Age

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The main purpose of clinical and electrophysiologic investigation in patients having complete atrioventricular (AV) nodal block is to differentiate between 2 different heterogeneous groups¹: one presenting with syncope or other bradycardia/tachycardia-related symptoms² and the asymptomatic group. The data available at the present time do not allow us to conclude which criteria is the best to distinguish the patient at risk for syncope in the latter group. Even when the site of block is in the proximal part of the His bundle¹ with a good response to parasympathetic blockade³ or to exercise,⁴ the junctional rhythm may not be stable enough, and Adam-Stokes attacks may occur.⁵ Some investigators believe that life-expectancy in symptomatic patients can be good.⁶ However, others have recognized that life-threatening arrhythmias may develop,⁷ and a prophylactic pacemaker should be implanted.⁸

This electrophysiologic investigation prospectively analyzes the prognostic value of the junctional recovery times in 15 young patients with complete AV nodal block. Twelve patients were women (mean age 21 years, range 5 months to 30 years). All patients were in New York Heart Association class I for dyspnea, except 1 patient who had dyspnea during feeding, probably because of the low heart rate considering his age (case 8). Retrospective history and electrocardiographic analyses allowed us to classify patients 3, 8, 9, 12, 14 and 15 as having congenital heart block. No previous documentation was available from the other patients. No data concerning connective tissue disease were available in the mothers of any patient. Chagas disease was excluded in all patients. The protocol consisted of: (1) determination of the level of AV block by His bundle recordings; (2) right ventricular stimulation in the apex of the right ventricle during 30 seconds with cycle lengths of 750, 650 and 550 followed by cessation of pacing to calculate the junctional and corrected junctional recovery times; (3) same stimulation protocol after administration of 1 or 0.04 mg/kg of atropine intravenously; (4) analyses of ≥ 10 cycles after cessation of pacing and QRS morphology; and (5) follow-up every 6 months.

The site of heart block was localized as proximal to the bundle of His, suggestive of AV nodal block in all patients. We found no linear correlation between the cycle length of the spontaneous escape rhythm and the junctional recovery times. In all patients the first pause was the longest one. Secondary pauses were not ob-

served. An inverse correlation between the pacing rate and the pause was found. The faster the pacing rate, the longer the pause was produced. Atropine shortened the junctional recovery times in all patients except patient 2. Control and atropine mean values for junctional recovery times and corrected junctional recovery times are listed in Table I.

The follow-up period ranged from 23 to 78 months (mean 53 ± 18). Three patients (cases 2, 3 and 13) became symptomatic during follow-up, at 12, 26 and 13 months, respectively, after the electrophysiologic study. Patient 8 was the only symptomatic patient at the beginning of the study (heart failure). All 4 patients underwent implantation of a permanent pacemaker. Of the remaining 11 asymptomatic patients, 7 had at least 1 value of the junctional recovery times > 2 times lower than the cycle length of the junctional escape rhythm (values between 260 and 860 ms). All 4 symptomatic patients had values of the corrected junctional recovery time > 260 ms. Four of 11 asymptomatic patients also had corrected junctional recovery time > 260 ms after administration of atropine (values between 260 and 860 ms). Patients with and without symptoms did not differ in relation to age, control heart rate, junction and corrected junctional recovery time before and after atropine. Patient 2 had the longest corrected junctional recovery time (3,020 ms) and was the only one to develop syncope during follow-up. However, patients 5 and 9 had a very long corrected junctional recovery time after atropine (860 and 760 ms, respectively) and remained asymptomatic. Patient 9 had 2 pregnancies without complications. All patients showed a permanent form of complete heart block in the follow-up.

The effect of overdrive suppression on the subsidiary escape pacemaker has been the subject of several studies.^{3,9} Narula³ found normal values of corrected junctional recovery time after administration of atropine of > 200 ms. In asymptomatic patients the values were ≤ 200 ms. He suggested that the measurement of the junctional recovery times was a reliable method to recognize patients at risk of syncopal attacks. Our results partially conflict with this assumption. All 4 symptomatic patients had abnormal corrected junctional recovery time after atropine, defined by Narula³ as a value ≥ 260 ms. However, 4 of the 11 remaining asymptomatic patients also had an abnormal corrected junctional recovery time after atropine (sensitivity 100%, specificity 63% and predictive accuracy 73%). These results suggest that the junctional recovery time has a good predictive accuracy for identifying patients with complete AV nodal block who are at risk of developing symptoms. Otherwise, until now, 4 patients (with false-positive results) did not develop symptoms,

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reflecting a poor specificity of this method (63%). In our study, all patients had junctional recovery time ≥ 200 ms, including the 11 asymptomatic patients. Similar results were found by Benson et al.¹⁰ We believe that the large spread of different values of junctional recovery times reflects the unrelated correlation between grade of subsidiary pacemaker inhibition imposed by pacing over-

drive and symptoms developed. The spread values demonstrate the limitation of this test.

Thus, there is no clear prognostic value in the findings of an abnormal corrected junctional recovery time after administration of atropine. However, patients with values similar to our patient 2 should be considered an exception. Because the incidence of syncope was relatively low

TABLE I Clinical Features and Results of the Junctional Recovery Times in 15 Patients with Complete Atrioventricular Nodal Block

Case	Age (yr) & Sex	Etiol. Heart Block	Symptoms During FU	Control				Atropine				Pacemaker Implant. (mos)	Total Follow-Up (mos)
				SCL	PCL	JRT	CJRT	SCL	PCL	JRT	CJRT		
1	28F	—	0	1,220	750	1,920	700	850	750	980	130	0	76
				1,220	650	1,940	720	860	650	960	100		
				1,200	550	2,060	860	850	550	980	130		
				1,480	750	1,520	40	1,380	750	1,520	140		
2	25F	—	Syncope	1,480	650	4,080	2,600	1,390	650	3,940	2,550	+12	71
				1,480	550	5,560	4,080	1,420	550	4,440	3,020		
				1,560	750	1,400	+160	860	750	1,010	150		
				1,570	650	3,260	1,690	960	650	1,280	320		
3	18F	CHB	Fatigue	1,620	550	3,730	2,110	980	550	1,320	340	+26	68
				1,460	750	1,720	260	830	750	980	150		
				1,440	650	2,960	1,520	840	650	1,000	160		
				1,500	550	3,720	2,220	860	550	1,120	260		
4	26F	—	0	1,490	750	1,780	290	980	750	1,680	700	0	64
				1,480	650	3,820	2,340	960	650	1,740	780		
				1,480	550	5,600	4,120	980	550	1,840	860		
				1,380	750	1,480	100	880	750	900	20		
5	30F	—	0	1,420	650	1,800	380	860	650	980	120	0	59
				1,480	550	2,020	540	860	550	980	120		
				1,560	750	1,700	140	800	750	880	80		
				1,520	650	1,720	200	840	650	900	60		
6	30F	—	0	1,520	550	1,800	280	760	550	900	140	0	55
				1,160	750	1,080	+80	1,000	750	1,180	180		
				1,260	650	1,600	340	980	650	1,320	340		
				1,260	550	1,750	490	960	550	1,320	360		
7	24M	—	0	1,800	750	3,360	1,560	1,280	750	1,880	600	0	47
				1,860	650	5,560	3,700	1,260	650	1,950	690		
				1,780	550	9,520	7,740	1,220	550	1,980	760		
				1,460	750	2,000	540	980	750	960	+20		
8	20F	CHB	0	1,570	650	2,080	510	960	650	970	10	0	47
				1,610	550	2,030	420	1,040	550	1,230	190		
				1,820	750	4,430	2,520	1,010	750	980	+30		
				1,870	650	6,740	4,870	960	650	960	0		
9	29F	—	0	1,670	550	7,280	5,610	980	550	980	0	0	45
				960	750	1,320	360	850	750	900	50		
				1,000	650	2,280	1,280	830	650	1,180	350		
				1,000	550	4,100	3,100	850	550	1,220	370		
10	2F	CHB	0	1,400	750	1,720	320	1,260	750	1,480	220	0	78
				1,400	650	1,780	380	1,300	650	1,600	300		
				1,400	550	6,080	4,680	1,360	550	1,590	230		
				1,400	750	5,320	3,920	760	750	920	160		
11	24F	—	Fatigue, dizziness	1,440	650	4,880	3,440	780	650	920	140	0	23
				1,400	550	4,400	3,000	820	550	960	140		
				1,480	750	1,880	400	960	750	1,020	60		
				1,480	650	2,040	560	960	650	1,100	140		
12	17F	CHB	0	1,480	550	4,840	3,360	960	550	1,100	140	0	27
Mean	21			1,380	750	2,170	730	980	750	1,150	170		53.2
				± 230		± 1,207	± 1,100	± 190		± 325	± 202		
				1,470	650	3,100	1,640	980	650	1,390	400		
				± 220		± 1,600	± 1,460	± 185		± 780	± 630		
				1,460	550	4,300	2,840	990	550	1,460	470		
				± 220		± 2,260	± 2,180	± 195		± 885	± 730		

* Pacemaker implanted immediately after electrophysiologic study.

CHB = congenital atrioventricular heart block; CJRT = corrected junctional recovery time; Etiol. = etiology; FU = follow-up; Implant. = implantation; JRT = junctional recovery time; SCL = spontaneous cycle length of the junctional escape rhythm; PCL = paced cycle length.

and mortality was zero, treatment decisions should be based on clinical symptoms.

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Seasonal Variation in Occurrence of Acute Atrial Fibrillation and Relation to Air Temperature and Sale of Alcohol

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Atrial fibrillation (AF) is the most common acute tachyarrhythmia encountered in everyday clinical practice. Although it may occur in healthy subjects, most cases are related to hypertensive, coronary or valvular heart disease, or to primary cardiomyopathy.^{1,2} The factors precipitating individual attacks are less well-studied, but include heavy use of alcohol.^{1,2} In a recent study of 100 consecutive patients with new-onset AF,² we found 2 to 3 times higher admission rates in winter than in summer, suggesting seasonal variation in the triggering factors. We therefore recorded the date of onset of acute AF in each patient presenting over the next year and studied the rate of the monthly admissions for AF in relation to ambient temperature and sale of alcohol in our area.

A total of 286 patients (205 men and 81 women, aged <65 years [mean 51]) presented with acute-onset AF in the emergency department of Helsinki University Central Hospital between January 1 and December 31, 1986. Nine were unaware of the time their current arrhythmia had started and were excluded from the subsequent analyses. The number of all emergency admissions for medical reasons during the study year was 10,130.

The mean monthly air temperatures in the city of Helsinki in 1986 (Figure 1) were obtained from the Institute of Meteorology. The value of monthly sales of alcohol in the area served by our hospital (Uusimaa province, population 1.1 million) was obtained, in retrospect, from statistics kept by The Finnish State Alcohol Company, which holds a monopoly of trade in alcohol in Finland. These data (Figure 1) therefore cover all except tax-free sales in 1986.

Admissions for acute AF (Figure 1) totaled 68 over the 4 warmest months (May to August), whereas the

rates were 109 and 102 during the first and last third of the year, respectively (chi-square 10.344, $p = 0.006$). During the same year, the number of all acute medical admissions was 3,120 from January through April, 3,442 from May through August and 3,568 from September through December (chi-square 31.68, $p = 0.000$). Time series analysis of the data (cross-correlation) verified a linear inverse relation between the rate of admissions for AF and the mean monthly temperature at lag 0 month ($r = -0.68$, $p = 0.016$). This correlation remained of practically equal magnitude even when the AF admission rate was calculated per 1,000 acute medical admissions in each respective month ($r = -0.64$, $p = 0.025$).

A linear regression model ($y = c + ax_1 + bx_2$), with the number of admissions for AF as the dependent variable (y) and the mean monthly temperature and sale of alcohol as independent variables (x_1 and x_2), was fitted to the data with the least-squares method. The fit was statistically significant ($F = 8.18$, $p = 0.009$), and the model explained two-thirds of the variation in the AF admission rate (multiple $R^2 = 0.65$). Standardized coefficients were -0.74 for the effect of temperature ($p = 0.004$) and 0.44 for the effect of alcohol sale ($p = 0.058$).

Although our study cannot prove any causal relations, it suggests that cold weather should be included among the factors promoting attacks of acute AF, at least in a middle-aged population. Exposure to cold increases sympathetic drive, peripheral arterial resistance, systolic blood pressure, central blood volume and ventricular filling pressure.³ These changes are notoriously capable of worsening myocardial ischemia and heart failure and they could increase left atrial distention and thus its propensity to fibrillate even in other conditions.^{3,4} Admittedly, indirect effects such as cold-induced aggravation of respiratory diseases, changes in living conditions, lifestyle and nutrition, and differences in occupational and leisure activities may also contribute. Seasonal variation in the incidence of cardiac arrhythmias has not been previously

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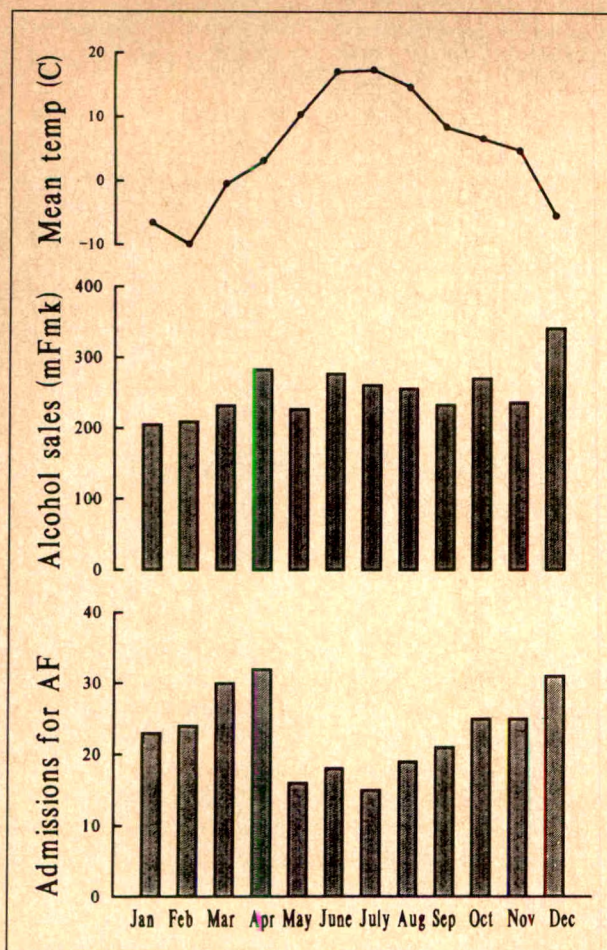


FIGURE 1. The number of admissions for acute atrial fibrillation (AF) per month, the value of monthly alcohol sales in millions of Finnish marks (mFmk) and the mean monthly air temperature in degrees of Celsius from January to December 1986.

proposed, but there are scattered data to indicate that exposure to cold may precipitate ventricular dysrhythmias both in health and in disease.^{5,6} Epidemiologic studies have shown that morbidity and mortality from coronary heart disease manifest seasonal variation with a

peak in winter and a trough in summer in cold and temperate zones.^{3,4} This pattern is reminiscent of the one found in the present study, which suggests that the basic underlying mechanisms may be similar.

Our investigation has certain limitations that should be considered in the interpretation of the data. The study was hospital-based and therefore the occurrence of asymptomatic or nonsustained episodes of AF could not be assessed. The data should be otherwise representative, however, because our hospital is by far the largest referral center in the province of Uusimaa and also because patients contacting private doctors or community health centers for acute-onset tachyarrhythmias are, as a rule, sent to the hospital in our area. We could not ascertain whether the size of the population at risk remained constant throughout the study period. It is extremely unlikely, however, that changes in the population size could explain the variation in admissions for AF, because similar variation was not found in the number of all emergency admissions for medical reasons. In fact, the rate of all medical admissions was lowest in the first third of the year, when the number of admissions for AF was highest.

The value of alcohol sales in our province was the only indicator available to us of monthly variation in alcohol consumption by the local population. It had a direct and temperature-independent linear relation to the rate of admissions for AF. Even though this association did not quite reach the conventional limit of statistical significance, and although the value of alcohol sale is not a perfect surrogate for the real volume of ethanol consumed, we think that these data are in reasonable harmony with the concept of alcohol as a risk factor for AF.^{2,4}

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Risk Factors for Atrial Fibrillation After Coronary Artery Bypass Grafting

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Atrial fibrillation (AF) and other supraventricular tachyarrhythmias have been shown to occur in almost 30% of patients who have undergone coronary artery bypass grafting (CABG).¹⁻³ Causes may include

direct surgical trauma to the atrial conductive network, postoperative irritative pericarditis, abrupt β -blocker withdrawal or inadequate atrial protection during cardiopulmonary bypass.⁴ Risk factor profiles for the development of AF after CABG have been compiled without a consistent pattern emerging.^{5,6} The purpose of this study was to evaluate possible contributing risk factors for the development of AF in a large cohort of patients immediately after CABG.

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TABLE I Complications and Supraventricular Tachyarrhythmias

	Total	SVT (%)	Non-SVT	p Value
Previous CABG	16	4 (25)	12	NS*
Pericarditis	31	8 (26)	23	NS
Perioperative MI	45	4 (29)	32	NS
History of AF	25	7 (28)	18	NS
Reexploration	12	4 (33)	8	NS

* Not significant.

AF = atrial fibrillation; CABG = coronary artery bypass grafting; MI = myocardial infarction; NS = not significant; SVT = supraventricular tachyarrhythmia.

Prospective analysis of consecutive patients immediately after elective CABG were studied. Patients undergoing concomitant cardiac procedures such as left ventricular aneurysm resection, valve repair or replacement, septal defect repair, and so forth, were excluded before the study. Patients with preexisting valvular heart disease or congestive heart failure also were excluded. The anesthetic and surgical techniques were similar for all patients. Patients who experienced an episode of sustained supraventricular tachyarrhythmias postoperatively were grouped for study. Sustained supraventricular tachyarrhythmias were defined as episodes lasting ≥ 30 seconds; however, most were persistent, necessitating antiarrhythmic therapy. All patients were maintained on a heart rhythm monitor with arrhythmia detection capabilities for ≥ 5 postoperative days. The usual hospitalization period was 7 to 9 days.

Patients who had postoperative complications such as perioperative Q-wave myocardial infarction, thoracic reexploration and clinical pericarditis were identified and analyzed separately. Clinical pericarditis was diagnosed by an audible pericardial friction rub after the removal of all chest tubes, associated symptomatology and treatment with anti-inflammatory agents. Patients with a prior history of atrial dysrhythmias but normal sinus rhythm at the time of surgery or previous coronary revascularization were also evaluated separately.

The remaining population was divided into the supraventricular and nonsupraventricular tachyarrhythmia groups. Factors analyzed to detect differences between groups were (1) preoperative characteristics: age, gender, history of myocardial infarction; and (2) operative characteristics: number of grafts, aortic cross-clamp time, creatine kinase peak, hemoglobin and hematocrit on the third postoperative day and complications during and after surgery.

The study data were analyzed with descriptive statistics including mean \pm standard deviation, and frequency distributions. Student's *t* and chi-square statistics were used to test the statistical significance of group differences.

The hospital course of 418 consecutive patients admitted for elective CABG were followed. Sustained postoperative supraventricular tachyarrhythmias occurred in 122 patients (29%). Of these, AF occurred in 85% ($n = 104$), followed by undefined in 9% ($n = 11$) and atrial flutter in 6% ($n = 7$). Reviewing this group for incidence of supraventricular tachyarrhythmias and the following conditions—previous CABG, history of preoperative AF, clinical pericarditis and perioperative myocardial

TABLE II Operative Characteristics

Factor	Groups		p Value
	Nonsupraventricular Tachyarrhythmia ($n = 205$)	Supraventricular Tachyarrhythmia ($n = 86$)	
Aortic cross clamp time (minutes)	41 (13)*	40 (16)	NS
Hemoglobin (g/dl) [†]	10 (1)	9 (2)	NS
Hematocrit (%) [†]	29 (3)	27 (5)	NS
Creatine kinase (U/ml)	763 (607)	877 (824)	NS
No. of bypasses	2.5 (1)	2.5 (1)	NS

* standard deviation.

[†] Third postoperative day.

NS = not significant.

infarction—we found that there were no statistical differences between or among conditions (Table I). After controlling for these conditions, 291 subjects remained. The incidence of supraventricular tachyarrhythmias in this group of 291 subjects was identical to that of the original 418 patients at 29% ($n = 86$).

The preoperative medications were studied in 152 patients: 66 were taking a β blocker that was discontinued the day of surgery and not reinstituted after surgery unless for the control of supraventricular tachyarrhythmias. Although the incidence of sustained supraventricular tachyarrhythmias was greater than that in other groups at 36% ($n = 24$), it was not significant.

The number of grafts, aortic cross-clamp time, creatine kinase peak, hemoglobin and hematocrit on the third postoperative day were nearly equivalent in both the supraventricular tachyarrhythmia and nonsupraventricular tachyarrhythmia groups (Table II). The history of a preoperative Q-wave myocardial infarction also did not impact the onset of supraventricular tachyarrhythmias.

These dysrhythmias were distributed equally among men and women. Age proved to be a statistically significant risk for the development of supraventricular tachyarrhythmias in these patients. The age for all subjects with a supraventricular tachyarrhythmia was mean \pm standard deviation 65 ± 8 years, whereas the age for the nonsupraventricular tachyarrhythmia group was 61 ± 11 years ($p < 0.001$).

There was a consistent incidence of AF among all subgroups. Previous studies of supraventricular tachyarrhythmia after CABG have excluded these complications as causes contributing to AF. It was surprising that these complications, even the most severe cases of pericarditis in which patients developed clinical symptoms requiring therapy, were found to be noncontributory. If inflammation and irritation of the thin-walled atria caused AF, there would be reason to anticipate a greater incidence in the worst cases. The incidence of AF among groups studied was so uniform that even a small group of patients with a history of AF and sinus rhythm at the time of surgery had no significantly greater frequency than the nonsupraventricular tachyarrhythmia group.

The possible effect of a low hemoglobin and hematocrit on the third postoperative day was studied. The third day was selected because these blood indexes are often stabilized by this time and the occurrence of these dysrhythmias peak during this period.^{1,7} Although the mean hemoglobin and hematocrit for all patients were abnormally low, they did not contribute to the onset of AF.

Tchervenkov et al⁴ proposed that inadequate atrial protection during cardiopulmonary bypass may prolong atrial ischemic time and contribute to AF after surgery. However, the development of AF within the first 24 hours of acute myocardial infarction is also thought to be ischemia,⁸ but AF only infrequently occurs within the first 24 hours after CABG.¹ Also, complicated or more traumatic surgery evidenced by a prolonged aortic cross-clamp time, increased number of bypasses, higher creatine kinase levels, or a significant perioperative myocardial infarction pose no greater risk for the development of AF.

The abrupt cessation of a β blocker on the day of surgery has also been implicated as a possible mechanism in the pathogenesis of supraventricular tachyarrhythmias in this setting.⁹ However, in the 152 patients whose pharmacologic therapy was followed in this study, β -blocker withdrawal did not appear as a risk factor. There is a strong possibility that abrupt β -blocker withdrawal syndrome may produce a physiologic environment for the development for tachyarrhythmias but not specifically rapid AF. It is recognized as a limitation that many

factors may play a role such as the kind of β blocker, dose and drug half-life.

The present study demonstrates that, with the exception of age, the onset of AF during the early postoperative course after CABG is enigmatic and continues to occur in many of these patients.

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Efficient Estimation of the Heart Period Power Spectrum Suitable for Physiologic or Pharmacologic Studies

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The standard deviation of the normal RR intervals (SDNN) computed over 24 hours predicts mortality after myocardial infarction.¹ The power spectrum of heart period or of instantaneous heart rate, calculated over intervals of 2 to 15 minutes, is used to assess autonomic nervous system activity: Energy in the 0.04- to 0.15-Hz band reflects both parasympathetic and sympathetic activity, and energy in the 0.15- to 0.40-Hz band reflects pure parasympathetic activity.² The prognostic

significance of 24-hour SDNN has stimulated interest in computing heart period power spectra for 24-hour periods. Previous computational approaches to the 24-hour heart rate power spectrum used the fast Fourier transform (FFT) to analyze the entire 24-hour period in toto.^{3,4} We report a practical approach for computing heart period or heart rate power spectra over 24-hour periods by analyzing the data in 5-minute segments. This approach has the advantages of permitting physiologic and pharmacologic studies and requiring fewer assumptions in dealing with "noisy" or arrhythmic segments.

The 24-hour recording is digitized and automatically processed using a Marquette 8500 Holter Analysis System. The time of onset of each QRS complex is defined, and each complex is classified as a normal QRS, an atrial or ventricular premature complex, or noise automatically by the computer and verified by a technician. The annotated file is then transferred to a Sun work station for further editing and calculations.

The 24-hour period is divided into consecutive, non-overlapping 5-minute segments and the following com-

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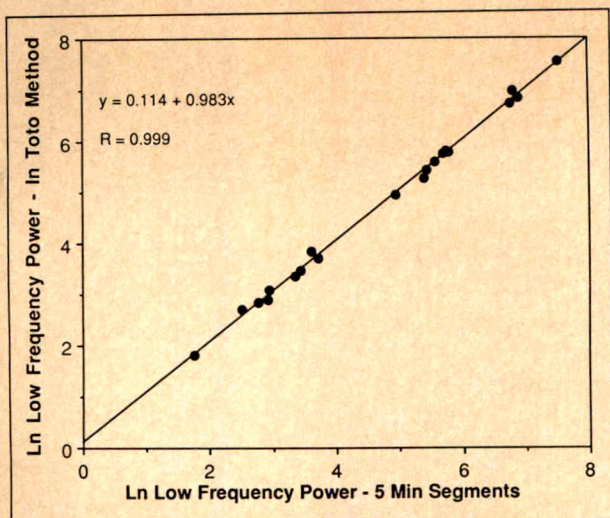


FIGURE 1. The correlation between the 2 methods of computing low frequency power was 0.999 ($p < 0.001$). The regression equation has an intercept not different from 0 and a slope not different from 1, indicating nearly identical results for the 2 methods. A log-log plot was done to accommodate the wide range of values. Ln = natural logarithm.

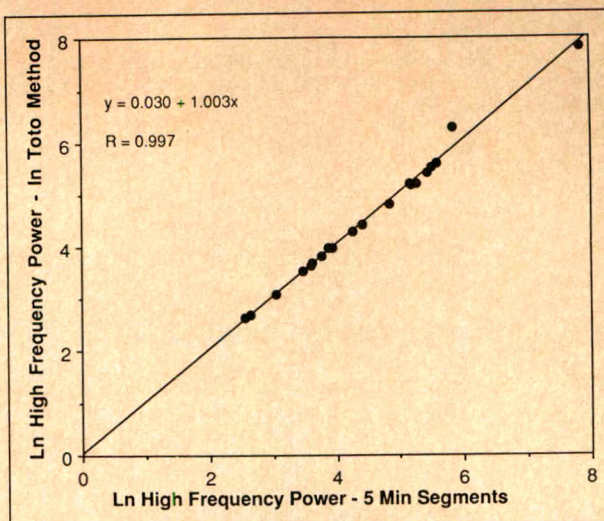


FIGURE 2. The correlation between the 2 methods of computing high frequency power was 0.997 ($p < 0.001$). The regression equation has an intercept not different from 0 and a slope not different from 1, indicating nearly identical results for the 2 methods. A log-log plot was done to accommodate the wide range of values. Ln = natural logarithm.

putations are performed for each segment: An instantaneous heart period function is sampled at 292-ms intervals, and smoothed using a 584-ms wide boxcar filter to provide 1,024 data points per segment.⁵ (To analyze heart rate variability, an instantaneous heart rate function can be sampled instead, without any other changes in the procedure.) When noise or atrial or ventricular premature complexes are encountered, the preceding and succeeding RR interval are excluded from the sampling and the instantaneous heart period function is estimated by linear interpolation. We require that $\geq 80\%$ of the RR intervals in a 5-minute segment be NN intervals; otherwise the segment is excluded. Then, the mean NN interval is subtracted from the sampled heart period data, a Hanning window is applied, and a FFT is computed.⁵ The resulting absolute 5-minute power spectra are corrected for attenuation resulting from the sampling³ and the Hanning window⁶ and averaged. The frequency range of the power spectra, 0.003 to 0.800 Hz, encompasses the frequencies of interest.

Theoretical considerations suggest that these 2 computational methods—the 24-hour in toto FFT, and the averaged spectra of 5 minute segments—should yield similar results. To confirm this theory, we compared the 2 approaches on twenty 24-hour Holter recordings that were used previously to compare time and frequency domain measures of cardiac parasympathetic activity.⁷ These tapes were not selected for freedom from noise or ectopy. The same digital annotated file was used to compute low, the 0.04- to 0.15-Hz band, and high frequency power, the 0.15- to 0.40-Hz band, by both methods. Natural logarithms of the power values were analyzed because of the skewness of the distributions. Figures 1 and 2 demonstrate the striking concordance between the 2 approaches. Regression analysis showed that neither fitted regression line was significantly different from the line of identity (intercept equal to 0 and slope equal to 1:

F ratio = 2.77, degrees of freedom = 2 and 18, $p > 0.05$ for the log of low frequency power; F ratio = 1.87, degrees of freedom = 2 and 18, $p > 0.10$ for the log of high frequency power). The 2 methods were most discordant for tape 10, which had the largest number of 5 minute segments excluded for ectopy or noise.

There are many theoretical problems encountered in computing the frequency spectrum of heart rate data, and any method must be a compromise between rigor and practicality. Our noise rejection criteria allow consistent processing of almost all tapes, and avoid long periods of arbitrary interpolation. The noise threshold was chosen in an effort to balance the competing objectives of minimizing both interpolation and segment rejection. Eighty percent is the most stringent criterion that yields both consistent results and a large fraction of accepted segments. Detrending and more complex filtering of the heart period signal were omitted without creating problems; the changes in the power spectrum produced by such simplifications lie outside of the frequency regions with which we are concerned.

For 24 hours of heart period or heart rate data, the 5-minute segmental method we describe can be efficiently computed, requiring only 1/250th the memory of the in toto method. Computation of the heart period power spectrum for consecutive 5-minute periods permits assessment of changes in autonomic tone over short periods of time for physiologic or pharmacologic investigation. Our algorithm can be readily implemented on modern Holter processing computer systems to facilitate further research on spectral components of heart period variability.

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Transvenous Atrial Septal Defect Occlusion by the Buttoned Device

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Transvenous occlusion of atrial septal defect (ASD) was first described by King and Mills¹ in 1976. Their device was too bulky to be applicable to children. Since that time other single-² or double-disk devices^{3,4} have been applied for the occlusion of ASDs. The "buttoned" device is the smallest available ASD-occluding device, because it requires an 8Fr introducing sheath. The efficacy and the safety of the method have been shown only in the occlusion of experimental ASDs.⁵ We are reporting the first clinical applications in children.

The "buttoned device" is custom-made by us (ES). It consists of 3 parts: the occluder, the counter-occluder and the loading wire.

The experimental application of the method has been described elsewhere.⁵ However, we will describe the modifications required for human application.

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A consent form, written according to rules regulating custom-made devices for each country, is first signed. The patient is taken to the interventional cardiac laboratory after previous sedation with pediatric lytic cocktail (Demerol®, 2 mg/kg; Phenergan®, 1 mg/kg; Thorazine® 1 mg/kg; these drugs were rarely supplemented by intravenous Ketamine®, 1 mg/kg). The right femoral vein and the left femoral artery are entered percutaneously (venous access for the occlusion, arterial access for monitoring). The diagnosis of ASD is first confirmed. The stretched diameter of the defect is determined using an atrial septostomy balloon catheter (American Edwards). An 8Fr-long sheath (Cordis) is introduced under fluoroscopy in the left atrium. The patient receives 100 U/kg of heparin. An appropriate device is selected (devices are available in sizes 25 to 40 mm). The occluder is dipped in heparin solution (1,000 U in 20 ml of saline); it is folded and introduced into the long sheath, where it is advanced by a pusher catheter.

The occluder is released into the left atrium, where it is automatically expanded, and is pulled against the tip

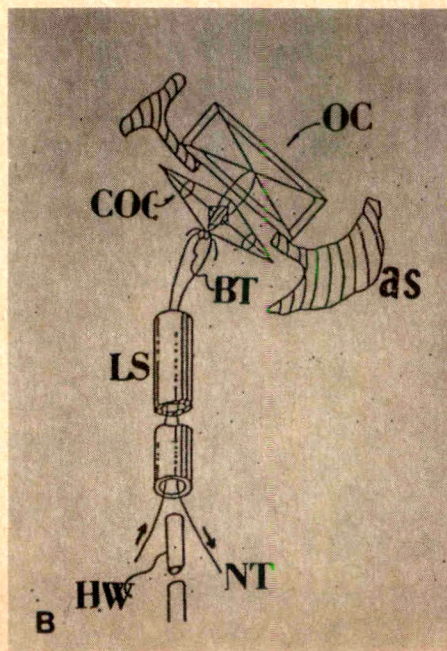
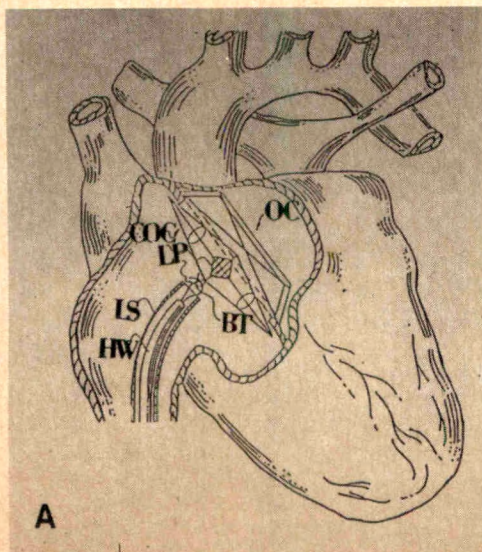


FIGURE 1. A, atrial septal defect occlusion. The occluder (OC) and the counter-occluder (COC) have been introduced independently across the defect and they are eventually buttoned. Buttoning involves piercing the occluder loop knot (button [BT]) through the counter-occluder latex piece. It is performed by applying traction on the loading wire using the left hand and pushing the counter-occluder with the tip of the long sheath (LS) simultaneously, using the right hand. **B**, the release of the buttoned device. The loading wire is cut outside the body and the hollow wire (HW) is pulled over the double nylon thread (NT). The nylon thread is then pulled as a single strand, releasing the device. as = atrial septum; LP = button loop.

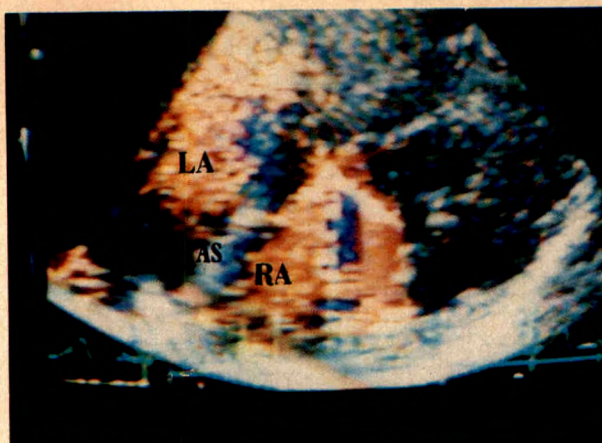
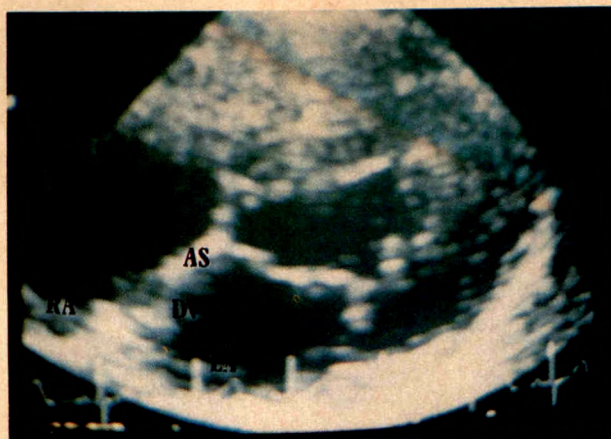


FIGURE 2. Left, 4-chamber view 1 year after buttoned device (DV) implantation; right, color-flow mapping on 4-chamber view 1 year after buttoned device implantation, demonstrating complete occlusion of the defect. AS = atrial septum; LA = left atrium; RA = right atrium.

of the long sheath until it becomes perpendicular to it. Subsequent to this, the long sheath-occluder complex is pulled until it catches on the left atrial side of the atrial septum, occluding the defect. The efficacy of the occlusion is confirmed by echocardiography and color-flow mapping or in their absence by pulmonary artery angiograms. The counter-occluder is introduced and advanced into the long sheath by the pusher catheter until it is released in the midright atrium. The position of the occluder on the atrial septum is maintained by immobilizing the end of the loading wire on the sterile drapes using a hemostatic clamp.

The buttoning is described in Figure 1A. Secure buttoning is checked by the parallel movement of the occluder and counter-occluder under different projections.

The release of the device is described in Figure 1B. Good occlusion of the defect is confirmed by color-flow mapping (Figure 2), or in its absence by oximetry and angiography.

These 3 patients (Table I) illustrate the effectiveness of the buttoned device in occluding human ASDs of the secundum type. Full occlusion was achieved in the last 2 patients and partial in the first. It is obvious that the method is not applicable to very large defects without adequate supporting tissue and a small left atrium.

The animal data were rather conclusive regarding the efficacy and safety of the occlusion of experimental ASDs by the buttoned device.⁵ However, several questions needed to be answered during human application regarding correct sizing of the defect, selection of the right size occluder and finally optimal guidance of the method.

Sizing of the defect was done in the first patient by echocardiography and it was inaccurate. It grossly underestimated the defect size. An inappropriate-sized occluder was selected and the method resulted in partial occlusion. Sizing in the last 2 patients was correctly performed by septostomy balloons, estimating the stretched diameter of the defect.

Selection of the appropriate occluder size was arbitrary. No conclusions can be drawn from the first patient,

TABLE I Patient Summary

Pt.	Age (yr)	Echo (mm)	Str. Diam. (mm)	Occ. (mm)	Qp:Qs (b.o.)	Qp:Qs (a.o.)	F-U (mos)
1	12	12	—	25	4.5	1.4	23
2	6	10	13	28	2	1	16
3	4	6	8	25	1.4	1	9

a.o. = after occlusion; b.o. = before occlusion; F-U = follow-up; Occ. = occlusion; Str. Diam. = stretched diameter.

because correct sizing was not performed. In the second patient, we used the recommendation of the animal data: a 12-mm occluder more than the diameter of the defect.⁶ However, it was obviously too small because it came through the defect. There may be interspecies differences in the distensibility of the atrial septal tissue. A 15-mm occluder-defect difference was used in the second patient and a 17-mm occluder-defect difference in the third. It is obvious that more patients are needed before firm recommendations are made.

Optimal guidance of the device is helpful to position and center the device correctly. Good fluoroscopy is necessary. The skeleton wires of the occluder and counter-occluder are well seen by fluoroscopy. Improvements are made to the button to make it visible as well. It is essential also that the long sheath is radiopaque. Echocardiography and color-flow mapping are helpful in the positioning and centering of the device. This was obvious in our animal work.⁵

The need for femoral vein cutdown to remove the device should be minimized with appropriate sizing of the defect. However, improvements in the device to make percutaneous occluder withdrawal possible are desirable.

All patients were discharged home within 24 hours and are well for up to 23 months of follow-up.

It is concluded that (1) the method is effective in closing some ASDs of the secundum type, (2) the device is safe to apply on follow-up, and (3) larger scale trials are justified.

Addendum: Sixteen patients with ASD secundum have been repaired with the buttoned device so far, uneventfully.

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Results of Laser-Assisted Balloon Angioplasty for Peripheral Arterial Obstruction Using a Lensed Fiber-Tip Delivery Catheter

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Percutaneous transluminal balloon angioplasty of obstructed iliac and femoral arteries is the therapy of choice in the management of selected patients with peripheral vascular disease. The advantages of percutaneous balloon angioplasty include a reduction in the morbidity of the revascularization procedure, a shorter hospital stay, and comparable 5-year patency rates when compared with surgical revascularization in selected patients.^{1,2} One of the limitations of balloon angioplasty is that a lesion must first be crossed with a guidewire. The inability to cross occlusions with a guidewire is the most common cause of failure of the procedure.

Laser angioplasty may have a role as an adjunct to balloon angioplasty by recanalizing lesions that cannot be traversed with a guidewire. The laser can create a channel through the arterial occlusion allowing the balloon catheter to be advanced across the lesion to further reduce the arterial stenosis. Early clinical trials of laser angioplasty in the peripheral arteries have demonstrated the unsatisfactory results obtained with single bare optical fibers used to deliver the laser energy due to the small channels created,³ and the high incidence of arterial perforation due to the sharp end of the laser fiber.⁴ In an attempt to

not only increase the size of the lumen created with the laser fiber but also reduce the risk of mechanical perforation, we have modified the distal end with a spherical lens that increases the spot size of the laser fiber and provides an atraumatic tip for the optical fiber. This report describes the first human clinical trials including 6-month follow-up of patients treated with a lensed fiber-tip laser delivery system designed for percutaneous revascularization of peripheral vascular obstructive lesions not amenable to conventional balloon angioplasty.

The 12 patients entered into the study included those with symptomatic lower extremity claudication scheduled to undergo elective balloon angioplasty. After informed consent was obtained patients were entered into the study protocol, approved by the hospital's clinical investigation committee, only if the obstructive lesion was unable to be crossed with an atraumatic angioplasty guidewire.

The average age of the patients included in the study was 70 ± 7 years (range 59 to 80). None of the patients had prior vascular surgery, and none had threatened limb loss. In the 12 patients, 14 lesions were attempted, of which 6 were total occlusions and 8 were subtotal occlusions by angiography. Three of the lesions were associated with dense calcification seen on fluoroscopy. One patient had a total occlusion of a common iliac artery and the remaining 13 lesions were located in the superficial femoral artery.

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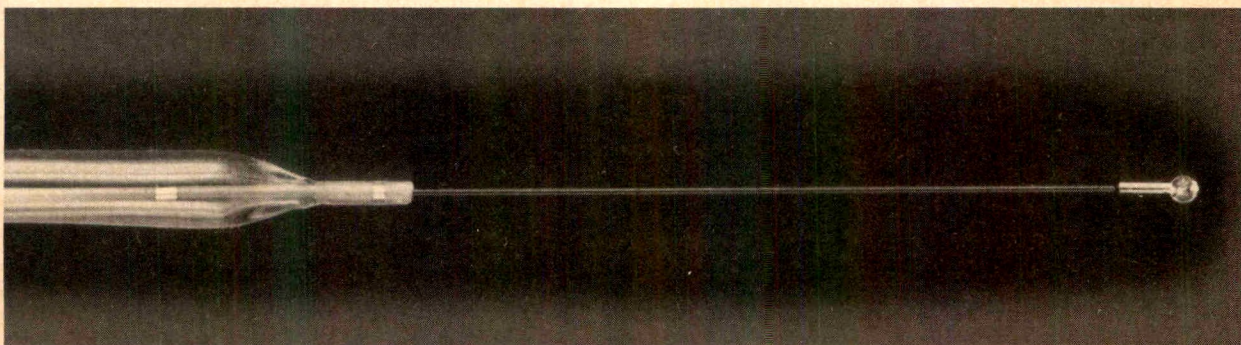


FIGURE 1. Laser-assisted balloon angioplasty catheter. The spherical lensed fiber may be advanced 6 cm ahead of the balloon catheter.

A baseline history, physical examination and ankle-brachial blood pressure index (ABI) were recorded on each patient. Ipsilateral femoral artery access was obtained with an 8Fr vascular sheath (Cordis, Miami, Florida) and 5,000 units of heparin was administered. An antegrade femoral artery approach was used for the superficial femoral artery lesions, and a retrograde approach was used in the single common iliac artery lesion. Baseline angiography of the lesion was performed and an attempt to cross the target lesion was made with a 0.035-inch guidewire (Wholey wire™, Advanced Cardiovascular Systems, Santa Clara, California).

After failing to cross the target lesion with the guidewire, the laser delivery catheter (Figure 1) was inserted through the arterial sheath and advanced to the lesion. The laser catheter consisted of a 7Fr balloon angioplasty catheter with a 300- μ m core diameter silica fiber placed through the central guidewire lumen (Schwartz™ balloon, Advanced Cardiovascular Systems, Santa Clara, California). Attached to the distal tip of the silica fiber was a 1.5-mm spherical silica lens. The optical fiber was freely movable within the guidewire lumen of the angioplasty balloon and could be advanced to a distance of 6 cm in front of the balloon catheter. The proximal end of the silica fiber was coupled to a neodymium-yttrium aluminum garnet pulsed laser (Lumonics, Ontario, Canada). Energy transmission through the lensed fiber was measured in air using a digital power meter before insertion into the patient.

The lensed fiber was advanced to be in contact with the lesion and attempts were made to cross the lesion without using laser energy which failed in every case. Energy was delivered with the lensed fiber in contact with the lesion at 0.5 J/pulse with a pulse duration of 100 μ s at 10 Hz in 2- to 5-second bursts. The lensed fiber was gently advanced during laser energy delivery until the lesion was crossed, arterial perforation occurred, or a predetermined maximum of 225 J of laser energy had been delivered. Intermittent injections of contrast material were performed to monitor the progress of the fiber through the target lesion. After the lensed fiber had successfully crossed the lesion, the balloon catheter was

TABLE I Laser Recanalization by Lesion Attempted

Lesion No.	Artery	Length (cm)	Success	Total Energy (J)	Baseline Stenosis (%)	Stenosis After Laser (%)	Stenosis After Balloon (%)
1	RSFA	1.5	+	30	99	90	0
2	RSFA	1	+	10	99	70	0
3	L SFA	1	+	80	99	75	5
4	L SFA	15	+	90	100	99	5
5	R Iliac	6	—	225	100	100	—
6	RSFA	28	+	75	100	99	20
7	L SFA	22	+	100	100	99	20
8	L SFA	2	+	50	99	99	10
9	RSFA	9	+	49	100	99	20
10	L SFA	2	+	104	99	60	10
11	L SFA	2	+	90	99	80	0
12	RSFA	2.5	+	100	99	70	0
13	RSFA	1	—	225	99	99	—
14	RSFA	8	—	225	100	100	—

L = left; R = right; SFA = superficial femoral artery.

advanced over the optical fiber and balloon dilation was performed. After laser-assisted balloon angioplasty, angiography was performed, and the catheter and sheath were removed. Postprocedure ankle-brachial blood pressure indexes were measured within 24 hours. Successful recanalization was defined as a reduction of the angiographic stenosis to <30% without arterial perforation. Clinical success was defined as an improvement in the ankle-brachial index by ≥ 0.1 from baseline, and an improvement in claudication symptoms.

Follow-up consisted of interval histories, physical examinations and ankle-brachial blood pressure measurements at 1, 3 and 6 months. Restenosis was defined as either return of symptoms to baseline levels or a decrease in the ankle-brachial index of ≥ 0.1 from the immediate postprocedure value.

Successful laser recanalization was accomplished in 11 of 14 lesions (Table I), and clinical success was obtained in 11 of 12 patients. The mean lesion length in successfully recanalized lesions was 7.8 ± 9.6 cm compared with 5.0 ± 3.6 cm in failed lesions, which was not statistically different. The total energy delivered to suc-

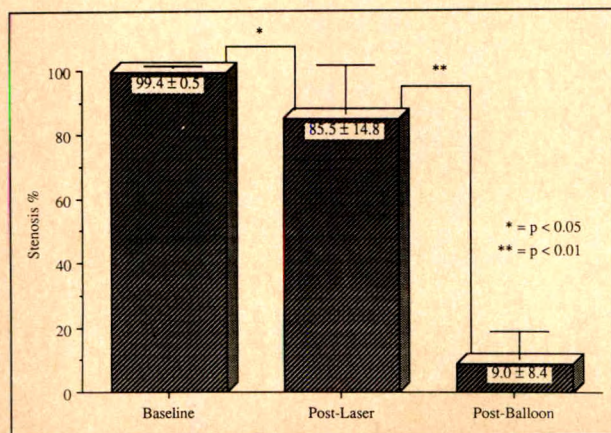


FIGURE 2. Angiographic stenosis in successfully recanalized lesions (n = 11) at baseline, after laser recanalization and after balloon angioplasty.

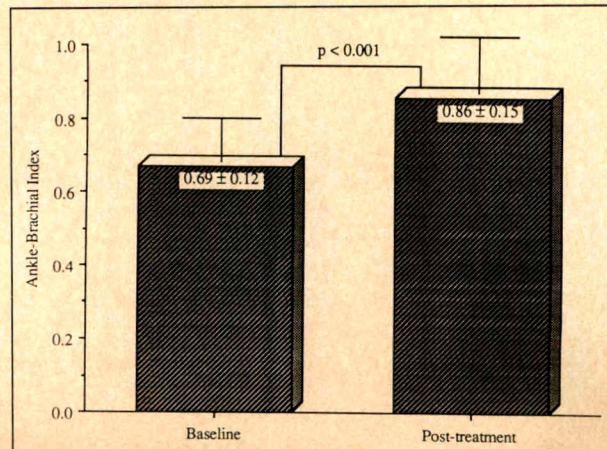


FIGURE 3. Ankle-brachial indexes in successfully recanalized patients (n = 11).

cessfully recanalized lesions was 70.7 ± 31.5 J (range 10 to 104) vs 225 J in each of the 3 failed lesions ($p = 0.001$). A significant reduction in angiographic stenoses in the successfully recanalized occlusions was obtained after laser recanalization alone as well as after balloon angioplasty (Figure 2). All of the patients with ≥ 1 successfully recanalized narrowing had clinical success as determined by both an improvement in their symptom of claudication and an increase in the ankle-brachial index by ≥ 0.1 (Figure 3).

There were no instances of arterial perforation or distal embolization in any patient. The patients reported no sensation of heat or discomfort during the laser procedure as has been reported during thermal laser procedures. Two of the failed lesions and 1 of the successfully recanalized lesions contained dense fluoroscopic calcification.

Restenosis occurred in 5 of 11 (46%) of the successfully recanalized lesions and was manifested by both a return of claudication symptoms to preprocedure levels and a decrease in the ankle-brachial index of ≥ 0.1 in all 5 patients. There were no significant differences among the variables measured including lesion length, total energy delivered, lesion stenosis either before or after treatment, or ankle-brachial indexes either before or after treatment between the lesions that recurred or those that remained patent.

This study demonstrated the safety and efficacy of a unique laser delivery system designed for adjunctive use with balloon angioplasty in lesions not amenable to conventional balloon angioplasty. We successfully recanalized 11 of 14 lesions, which resulted in clinical improvement in 11 of 12 patients without arterial perforation or distal embolization. An argument can be made that many lesions not able to be crossed with a soft, atraumatic guidewire such as the type used in our laboratory could be traversed with stiffer, more traumatic guidewires. It is our experience that these more traumatic techniques frequently result in intimal and medial dissections at the site of the arterial occlusion. The subintimal passage of the guidewire may lead to a balloon inflation in this false channel, resulting in a suboptimal balloon dilation.

The rounded 1.5-mm diameter spherical lensed fiber tip is an atraumatic device with which to cross occlusions. Preclinical trials with this laser delivery system in an atherosclerotic swine model have demonstrated the propensity for the spherical lensed fiber tip to select the native lumen in totally occluded arteries.^{5,6} We have also demonstrated that mechanical perforation of arteries is eliminated with the use of the spherical lensed tip, which remains a potential problem with bare fiber laser catheters.⁷ The lensed fiber also has a larger spot size than bare fibers, allowing a larger recanalized lumen to be created.

An advantage of this laser-assisted balloon angioplasty system is that once the obstructive lesion has been crossed with the laser device, the balloon catheter can be directly advanced over the optical fiber. This avoids the uncertainty and risk involved in recrossing lesions with guidewires after laser recanalization, which is required when using systems without integrated balloon dilation catheters.

The ability to transmit laser light directly to the target tissue is another advantage of using lensed fiber systems. This direct transmission of light allows specific laser-tissue interactions to occur such as preferential wavelength absorption by the target lesion,⁸⁻¹⁰ and enables the advantages of pulsed energy delivery to be exploited to avoid thermal damage to the tissue surrounding the target lesion. The delivery of energy in short pulses (shorter than the thermal relaxation time of the tissue) allows the ablation of tissue while minimizing the amount of heat accumulating in the tissue.¹¹

In conclusion, this laser-assisted balloon angioplasty system is safe and effective for recanalizing obstructive lesions not amenable to conventional balloon angioplasty. The role of laser angioplasty in vascular medicine needs to be determined, but it appears that this device may be a valuable adjunct to balloon angioplasty by allowing percutaneous revascularization in symptomatic patients who otherwise would be referred for surgical therapy or forced to live with their disability.

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Experience with a Newly Developed Pericardiocentesis Set

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Pericardiocentesis is a widely used therapeutic and diagnostic procedure. Although a limited number of pericardiocentesis sets are commercially available, none has been developed for use in children. This report describes experience with a newly developed pericardiocentesis set, specifically designed for pediatric patients.

The study group comprised 11 consecutive, unselected patients in whom pericardiocentesis was performed at Children's Hospital of Pittsburgh between December 1987 and February 1990. Clinical information and characteristics of pericardial fluids are listed in Table I in order of the patient's age. Their ages and body weights ranged from 1 day to 18 years (median 7 years) and from 3.1 to 59.7 kg (median 21.5), respectively. The presence of pericardial effusion was diagnosed by 2-dimensional echocardiography.

The most common etiology of pericardial effusion was that in association with a prolonged febrile course after cardiac surgery in 4 patients (nos. 3, 4, 6 and 11). In 3 of these the pericardial fluid culture was negative and

the etiology was ascribed to postpericardiotomy syndrome. The remaining patient had a positive culture for staphylococcus aureus and had an associated mediastinitis. Other etiologies included viral pericarditis in 2 patients (nos. 8 and 9), idiopathic pericarditis in a newborn (patient no. 2) with necrotizing enterocolitis, and myocardial dysfunction with congestive heart failure in 2: one with Kawasaki syndrome (no. 7) and another with restrictive cardiomyopathy 3 years after orthotopic heart transplantation (no. 10). In the remaining 2 patients, the pericardial effusion was related to trauma: a 1-day-old newborn (no. 1) with transposition of the great arteries developed pericardial tamponade in association with hemopericardium due to an iatrogenic perforation of the left atrium during cardiac catheterization; the other patient developed pericardial effusion after an automobile accident.

Pericardiocentesis was performed in the cardiac catheterization laboratory under fluoroscopic guidance in all patients except 1 (no. 9), in whom it was performed in the intensive care unit with 2-dimensional echocardiographic guidance. All but 2 patients (nos. 1 and 9) received a combination of meperidine 2 mg/kg, promethazine 0.5 mg/kg and chlorpromazine 0.5 mg/kg intramuscularly 30 to 45 minutes before the procedure or fentanyl citrate 1 mg/kg intravenously shortly before the procedure.

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TABLE I Clinical Data and Findings of Pericardial Effusion

Pt. No.	Diagnoses	Age	Weight (kg)	Pericardial Fluid				Catheter	
				Echo (mm)	Yield (cc)	Appearance	Culture	Out/In	Duration (days)
1	TGA LA perforation	1 day	4.4	>10	>500*	Blood	Negative	Out	
2	NEC Idiopathic PC	5 days	3.1	8	38	Serousanguinous	Negative	Out	
3	PA, VSD, MS, PPS	9 mos.	7.7	19	133	Serousanguinous	Negative	Out	
4	PA, HRV, FP, PC	2-10/12 yrs.	11.5	12	120	Serousanguinous	Staph. aureus	In	1
5	Abdominal injury Traumatic PE	2-10/12 yrs.	14.0	18	185	Serous	Negative	Out	
6	TGA, VSD, PS, BT RP, PPS	7 yrs.	21.5	23	290	Serousanguinous	Negative	Out	
7	Kawasaki, PC, MYO	7-2/12 yrs.	30.0	11	145	Viscous serous	Negative	Out	3
8	Viral PC	7-8/12 yrs.	19.5	20	170	Serousanguinous	Negative	Out	
9	Viral PC	8-3/12 yrs.	29.4	35	805	Serousanguinous	Negative	In	3
10	Heart transplant	15-11/12 yrs.	46.6	25	610	Serous	Negative	Out	
11	CT, VR, PPS	18 yrs.	59.7	33	100†	Serousanguinous	Negative	Out	
Median 7 yrs.			Median 21.5 kg	Mean 24	Mean 281				

* Reinfused to the venous line; † loculated.

BT = Blalock-Taussig shunt; CT = corrected transposition; FP = Fontan procedure; HRV = hypoplastic right ventricle; Kawasaki = Kawasaki syndrome; LA = left atrium; MS = modified Blalock-Taussig shunt; MYO = myocarditis; NEC = necrotizing enterocolitis; PA = pulmonary atresia; PC = pericarditis; PE = pericardial effusion; PPS = post pericardiotomy syndrome; PS = pulmonary stenosis; RP = Rastelli procedure; Staph. = staphylococcus; TGA = transposition of the great arteries; VR = prosthetic valve replacement; VSD = ventricular septal defect.

cedure. Most of the patients underwent the procedure in the supine position, while a few who had orthopnea were in the semi-sitting position. An electrocardiogram was monitored throughout the procedure.

The set consists of: (1) two 20-gauge-thin wall needles (4 cm and 7 cm in length for patients with an unusually thick chest wall); (2) a 0.025-inch J-tip Teflon®-coated guidewire, 50-cm long; (3) a 3Fr Teflon introducer, 27-cm long; and (4) a 5Fr polyethylene catheter, 20-cm long with a J-shaped curve at the tip (Figure 1). The tip of the catheter is tapered to a 4Fr size. There are multiple openings (0.025 inch) on the concave as well as on the convex sides of the catheter tip.

The subxyphoid area is prepped and draped to provide a sterile field. Lidocaine (1%) is infiltrated at the left costoxiphoid angle extending posteriorly and slightly superiorly. Using a sharp-pointed number-11-blade scalpel, a 2 to 3 mm stab wound is made at the site of the lidocaine infiltration (Figure 2A). The needle is attached to a 3-ml syringe containing a small amount of flushing solution and introduced into the stab wound, directed toward the left axilla with the needle advancing at an angle of 20 to 30° from the horizontal plane (Figure 2B). The operator may have a sensation of "popping" as the needle punctures the pericardium and pericardial fluid is aspirated. After confirmation of free aspiration of a small amount of pericardial fluid, the syringe is re-

moved. The guidewire is then advanced through the needle under biplane fluoroscopic guidance or by 2-dimensional echo imaging (Figure 2, C and D). Ideally, the guidewire is passed around the inferior portion of the heart into the posterior aspect of the pericardial space. Once the guidewire is in a satisfactory position, the needle is removed (Figure 2E). The combined introducer and catheter set is then passed over the wire. Initially, the introducer alone is manipulated by rotating or twirling it until the tip is in the pericardial space (Figure 2F). The catheter is then advanced over the introducer by similar manipulation until the catheter reaches as far as possible into the posterior pericardial space. The guidewire and introducer are subsequently removed while the drainage catheter remains in the pericardial space. A 3-way stopcock is attached to the catheter hub and drainage of the pericardial fluid is accomplished with a large syringe, usually of 30- or 50-ml capacity (Figure 2G).

In all cases, the procedure was successful and without complication. Only 4-cm needles were used and no patient in this series, even the 2 teenagers weighing more than 45 kg, required a longer needle (7 cm). Pericardial drainage ranged from 38 ml in a 5-day-old newborn to 800 ml in an 8-year-old boy with viral pericarditis (mean 281 ml). The nature of the pericardial fluid is listed in Table I. In most cases, it was either serous or serosanguinous. In the newborn infant who had left atrial perfor-

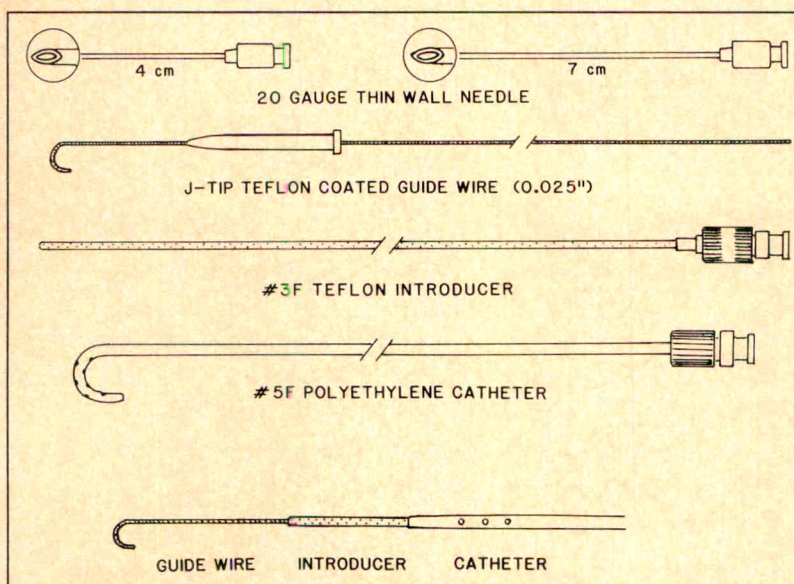


FIGURE 1. Diagrammatic illustrations of each component of the pericardiocentesis set (see text).

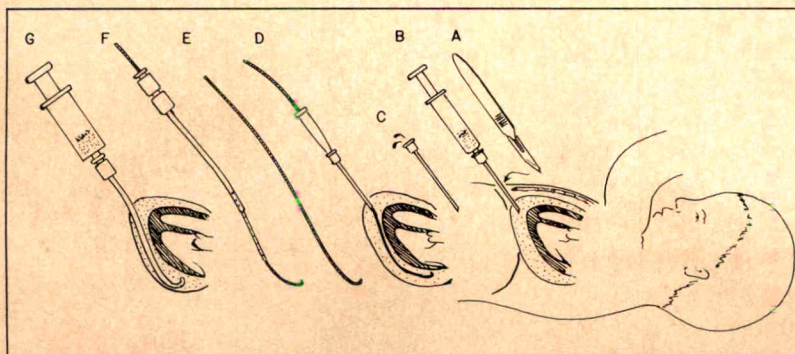


FIGURE 2. Sequence of the pericardiocentesis procedure (see text).

ration during cardiac catheterization, pericardiocentesis yielded pure blood, which was reinfused through a central venous line until the surgeon repaired the perforation. The patient had an uneventful course and subsequently had a successful arterial switch procedure. In 3 patients, a pericardial catheter was left in place for 1 to 3 days because of concern about the possibility of reaccumulation. An additional 50 to 150 ml of pericardial fluid was removed during this period. One patient had a culture-proven staphylococcal pericarditis in association with mediastinitis and required surgical intervention. The remaining 10 patients had negative bacterial cultures and did not require further surgical intervention for their pericardial effusion. All patients recovered without sequelae.

Although pericardiocentesis is a relatively straightforward procedure, complications related to it have been considerable, ranging from a nonproductive tap to death.¹⁻³ In recent years, the overall incidence of complications has decreased as accurate diagnosis and localization of pericardial effusion is readily made by 2-dimensional echocardiography and by computer tomographic scan.

Self-contained pericardiocentesis sets are now commercially available; however, they are primarily aimed at the adult population. The relatively large components are not suitable for safe use in children. The primary purpose of our study was to develop a dedicated pericardiocentesis set for the pediatric age group. Delicate maneuverability and precise placement of a drainage catheter into the limited pericardial space are of prime consideration in smaller patients with relatively smaller amounts of pericardial fluid.

Most commercially available pericardiocentesis sets include an alligator clip that is intended to monitor the electrocardiogram through the needle. The technique uses electrocardiographic changes to identify misplacement of the needle and direct contact with the atrium or ventricle. However, this technique is not only unreliable⁴ but also causes considerable distraction during the delicate maneuvers of the procedure itself. Therefore, capability for electrocardiographic monitoring through the needle was not incorporated in this set.

The drainage catheter is a relatively small, 5Fr-thin wall polyethylene catheter, which is flexible enough to be used for a newborn, yet large enough for even the older teenagers. The gentle J-shaped tip of the catheter is de-

signed to prevent inadvertent trauma to the myocardium. The number, placement and size of the side holes of this catheter are important for short- and long-term drainage.^{5,6} There are multiple holes on the convex and concave sides of the curved catheter tip, arranged to prevent occlusion by contact between the catheter and the pericardial or epicardial surfaces. The side holes, of 0.025-inch diameter, were large enough to drain effectively for up to 3 days in our 3 patients with serous or serosanguinous pericardial fluid. However, when purulent pericarditis is documented, open surgical drainage is recommended, even if the pericardiocentesis is successful in removing most of the fluid.

The small 3Fr Teflon introducer is easily passed over the guidewire into the pericardial space without the aid of a dilator. When the catheter is passed over this introducer, the entire system has a gentle taper from the wire diameter to the catheter diameter, as shown in Figure 1 (bottom), thereby eliminating the need for a separate dilation procedure. This set facilitates performing pericardiocentesis efficiently in a short period of time, particularly when emergency pericardiocentesis is needed.

In conclusion, our limited clinical trial with a newly developed pericardiocentesis set has shown its effectiveness and safety in a wide range of pediatric patients, from newborn infants to older teenagers. The set may help to reduce the complications related to pericardiocentesis. It also can be used as a short-term indwelling drainage catheter.

Acknowledgment: The pericardiocentesis sets for this study were provided by Cook Incorporated (Bloomington, Indiana). We gratefully acknowledge the technical assistance of Joseph Roberts of Cook Incorporated.

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Relation of Mean Pulmonary Arterial Wedge Pressure and Left Ventricular End-Diastolic Pressure

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The flow-directed, balloon-tipped catheter has facilitated the management of critically ill patients by providing a means of measuring right-sided cardiac pressures and output. In addition, it has been used to measure certain left-sided cardiac pressures. Hellemis et al¹ reported that a catheter effectively "wedged" in a pulmonary artery (PA) yielded blood that was fully saturated with oxygen and a pressure reflective of that in the left atrium. Subsequently, other investigators substantiated this observation, noting that an oximetrically confirmed PA wedge pressure was similar to left atrial pressure.^{2,3} In the absence of mitral valve disease, mean PA wedge pressure is similar to mean left ventricular (LV) diastolic pressure, but there is continuing confusion about the relation between mean PA wedge and LV end-diastolic pressures.⁴ In subjects without cardiac disease, mean left atrial pressure (and likewise mean PA wedge pressure) almost always approximates LV end-diastolic pressure⁵ and, therefore, can be used to assess LV filling. In contrast, these pressures may be disparate in subjects with cardiac disease.⁶ This study was performed to examine the relation of mean PA wedge and LV end-diastolic pressures in patients with and without cardiac disease.

From July 1978 to March 1990, diagnostic right and left-sided cardiac catheterization with simultaneous measurement of PA wedge and LV pressures was performed in 3,159 patients (1,643 men, 1,516 women, aged 50 ± 12 [mean \pm standard deviation] years). Patients were excluded from analysis if they had mitral stenosis ($n = 180$), mitral regurgitation ($n = 1,137$), a technically inadequate left ventriculogram (usually due to repetitive ventricular ectopic complexes) ($n = 378$), or a lack of oximetric confirmation that the right-sided heart catheter was effectively wedged (failure to aspirate blood with an oxygen saturation $\geq 95\%$) ($n = 992$). In the remaining 472 patients (263 men, 209 women, aged 48 ± 13 years), an oximetrically confirmed PA wedge and LV pressures were recorded simultaneously with stiff, large-lumen catheters (8Fr Goodale-Lubin and 8Fr pigtail, respectively).

Of the 472 patients, 43 had no evidence of cardiovascular disease; 230 had coronary artery disease (defined as $\geq 70\%$ luminal diameter narrowing of ≥ 1 large epicardial coronary artery); 51 had aortic valvular disease (regurgitation in 39, stenosis in 12); 53 had systemic arterial hypertension with electrocardiographic or echo-

cardiographic evidence, or both, of LV hypertrophy; and the remaining 95 had miscellaneous congenital, myocardial or pericardial abnormalities.

For the 472 subjects, mean PA wedge and LV end-diastolic pressures correlated well with one another ($r = 0.88$). However, they differed by ≥ 5 mm Hg in 133 (28%), and were ≤ 5 mm Hg in the other 339 (72%). For the 133 with a disparity of LV end-diastolic and mean PA wedge pressures, LV end-diastolic pressure was 20.4 ± 6.6 mm Hg and mean PA wedge pressure was 13.0 ± 5.2 mm Hg ($p < 0.0001$). LV end-diastolic pressure exceeded mean PA wedge pressure in 132 of the 133 patients. LV end-diastolic and mean PA wedge pressures differed ≥ 5 mm Hg in only 1 of the 43 patients (2%) without cardiac disease. In contrast, a disparity of LV end-diastolic and mean PA wedge pressures was noted in 31% of patients with coronary artery disease, 40% of those with systemic arterial hypertension and 53% of those with aortic valvular disease.

In the absence of mitral valvular disease, the pulmonary veins, left atrium and left ventricle communicate during diastole, forming, in essence, a common chamber. As a result, a properly confirmed mean PA wedge pressure is reflective of mean LV diastolic pressure. At the same time, many patients with cardiac disease have LV end-diastolic pressure that is distinctly greater than mean PA wedge pressure, predominantly because of a large *a* wave produced by atrial contraction into a relatively stiff, noncompliant ventricle.⁶ In these patients, LV end-diastolic pressure may substantially exceed mean PA wedge pressure. Indeed, 133 of our 472 patients (28%) had ≥ 5 mm Hg disparity between mean PA wedge and LV end-diastolic pressures, with the former being consistently lower in all but 1 patient.

Certain cardiac abnormalities were often associated with a disparity between LV end-diastolic and mean PA wedge pressures, including aortic valvular disease, hypertension and coronary artery disease, conditions that may be associated with reduced LV compliance and a prominent LV *a* wave.⁶ In contradistinction, LV end-diastolic and mean PA wedge pressures were similar in almost all subjects with normal cardiac function.

In summary, in patients with normal cardiac function, mean PA wedge pressure closely approximates LV end-diastolic pressure. However, these pressures may be dissimilar in patients with aortic valvular disease, systemic arterial hypertension and coronary artery disease, in whom LV end-diastolic pressure exceeds mean PA wedge pressure because of LV noncompliance and a prominent *a* wave. In patients with cardiac disease, mean PA wedge pressure cannot be used reliably to assess LV end-diastolic pressure.

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Ventricular Arrhythmias After Balloon Aortic Valvuloplasty

Kenneth M. Weesner, MD

Balloon dilation of congenital heart defects is being performed with increasing frequency. Although these procedures are generally safe, a number of complications can occur, including obstruction of leg vessels, bleeding and rarely reported episodes of sudden death.¹ Prolongation of the corrected QT interval (QTc) has been reported with pulmonary balloon valvuloplasty.² During surveillance after balloon aortic valvuloplasty, 4 patients with asymptomatic ventricular tachycardia were identified by Holter monitor recording.

Four patients underwent balloon aortic valvuloplasty for severe aortic stenosis between April 16, 1986, and June 15, 1989. The first patient, a 3.5-year-old, 17-kg boy, had an 80-mm Hg aortic gradient. The aortic valve was dilated with a 3-cm-long, 15-mm inflated diameter balloon

catheter, inflated twice at 3 atm for 10 seconds. After valvuloplasty, the aortic gradient was 40 mm Hg (50% reduction) and trivial aortic insufficiency was noted. A 24-hour Holter monitor was performed in the intensive care unit following dilation. After valvuloplasty, the Holter monitor documented a prolonged QTc interval and a 3-beat salvo of ventricular tachycardia (Figure 1, Table I). This patient has remained asymptomatic for 4 years with no change in transaortic gradient by Doppler echocardiography.

The second patient, a 6.5-year-old, 20-kg boy, had a 120-mm Hg peak gradient before treatment. The aortic valve was dilated with a 20-mm diameter, 3-cm-long balloon, which was inflated 1 time for 10 seconds at 3 atm. After valvuloplasty, the gradient was 25 mm Hg (79% reduction) and there was 3+/4 aortic insufficiency noted after the proce-

dures. Holter monitoring revealed prolongation of the QTc, frequent premature ventricular contractions, and 4 bursts of nonsustained ventricular tachycardia (Table I, Figure 1). The child has remained asymptomatic for 2 years of follow-up.

The third patient, a 7-year-old, 21-kg boy, had a 50-mm Hg peak aortic gradient before balloon valvuloplasty. The aortic valve was dilated with an 18-mm diameter, 3-cm-long balloon, inflated 3 times for 10 seconds at 3 atm. After valvuloplasty, there was a 10-mm Hg peak gradient across the aortic valve (80% reduction), and 2+/4 aortic insufficiency was noted. A 24-hour Holter monitor demonstrated a prolonged QTc interval, frequent premature ventricular contractions, and 5 episodes of nonsustained ventricular tachycardia (Table I, Figure 1). The QTc was normal at the end of Holter monitoring and no ectopy was identified. This patient has remained asymptomatic after 2 years of follow-up.

The fourth patient, a 9.5-year-old, 31-kg girl, had an aortic gradient of 90 mm Hg before valvuloplasty. The aortic valve was dilated with an 18-mm diameter, 3-cm-long balloon, with 3 inflations for 10 seconds at 4 atm. After dilation, the gradient was reduced to 42 mm Hg (53% reduction) and there was trace aortic insufficiency. Treatment with lidocaine was required before balloon valvuloplasty for ventricular ectopy. This was discontinued before leaving the catheterization laboratory and no ectopy was observed. With Holter monitoring, a prolonged QTc was recorded, as well as 5 episodes of nonsustained ventricular tachycardia and frequent premature ventricular contractions (Table I, Figure 1). This patient has remained asymptomatic after 9 months of follow-up.

Only 1 of these 4 patients had arrhythmias that required treatment in the catheterization laboratory. They were the only 4 patients to undergo aortic valvuloplasty during this period. While all 4 patients were monitored in the intensive care unit after the procedure, none had arrhythmias observed by nursing per-

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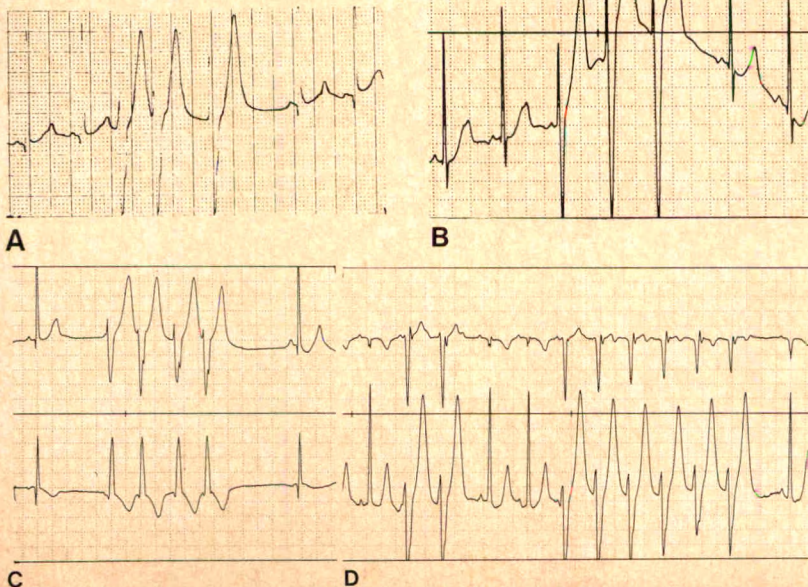


FIGURE 1. Representative tracings from Holter monitor recordings after valvuloplasty illustrate abnormalities identified and are presented in the order (A, B, C, D) that the patients were seen.

TABLE I QTc in Four Patients Before and After Balloon Aortic Valvuloplasty

Pt.	Before Catheterization	At Start of Holter Recording	At Time of VT (First Episode)	At End of Holter Recording
1	0.41 s	0.42 s	0.55 s (11 hrs)	0.38 s
2	0.41 s	0.48 s	0.52 s (12 hrs)	0.44 s
3	0.43 s	0.46 s	0.50 s (5 hrs)	0.41 s
4	0.40 s	0.55 s	0.50 s (4 hrs)	0.43 s

VT = ventricular tachycardia.

sonnel. At the end of Holter monitoring, no ventricular arrhythmias were noted, and a resting 12-lead electrocardiogram demonstrated a normal QTc before hospital discharge (Table I). None of these patients had any depolarization changes associated with valvuloplasty.

Sudden death has been reported to occur immediately after an apparently successful balloon dilation procedure.^{1,3} Because of this observation and the occurrence of sudden death in patients with severe aortic stenosis, I elected to monitor these patients intensively after balloon aortic valvuloplasty. Even though there apparently was a good hemodynamic re-

sult, and the children have done well both in short- and long-term follow-up, all 4 had ventricular tachycardia recorded between 4 and 18 hours after balloon valvuloplasty. My technique appears to be comparable to that reported by others, although this observation has not been previously reported.^{4,5} The etiology of these arrhythmias is unclear, however; all 4 patients had documented prolongation of the QTc interval, whereas both precatheterization electrocardiograms and those obtained before discharge showed a normal QTc and no arrhythmias. The results of this report suggest that close observation of patients after balloon aortic val-

loplasty is warranted, because ventricular tachycardia may occur.

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Neuroendocrine activity in congestive heart failure; 33D

Pharmacology of angiotensin-converting enzyme inhibitors as a guide to their use in congestive heart failure; 7D

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Cardiac catheterization laboratory—1990; 37F

Cardiovascular effects of iodinated contrast agents; 9F

Clinical cardiovascular magnetic resonance imaging; 41F

Clinical nuclear magnetic resonance spectroscopy: insight into metabolism; 45F

Contrast media safety: what do we know and how do we know it? 34F

Contrast media: the relation of chemical structure, animal toxicity and adverse clinical effects; 2F

Experimental contrast-associated nephropathy and its clinical implications; 18F

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Positron emission tomography and interventional cardiology; 51F

Role of magnetic resonance contrast agents in cardiac imaging; 59F

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Symposium: HMG CoA Reductase Inhibitors—A Five-Year Clinical Perspective

A multicenter comparison of lovastatin and probucol for treatment of severe primary hypercholesterolemia; 22B

Comparison of the effects of lovastatin and gemfibrozil on lipids and glucose control in noninsulin-dependent diabetes mellitus; 16B

Efficacy and tolerability of lovastatin in a six-month study: analysis by gender, age and hypertensive status; 1B

Expanded clinical evaluation of lovastatin (EXCEL) study: design and patient characteristics of a double-blind, placebo-controlled study in patients with moderate hypercholesterolemia; 44B

Extended clinical safety profile of lovastatin; 11B

Lovastatin and simvastatin prevention studies; 39B

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Calcium-channel antagonist effects of spironolactone, an aldosterone antagonist; 7K

Clinical update: spironolactone and altizide as monotherapy in systemic hypertension; 20K

Editorial overview; 3K, 39K

Editorial overview: European experience with spironolactone and thiazide diuretic as antihypertensive therapy; 18K

Effects of potassium-sparing/thiazide diuretic combination on cardiovascular reactivity to vasopressor agents; 14K

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Peripheral action of spironolactone: arterial elasticity; 9K

Peripheral action of spironolactone: plethysmographic studies; 12K

Relation of cardiovascular disease to potassium and magnesium deficiencies; 44K

Role of magnesium in cardiac tachyarrhythmias; 47K

Short- and long-term mechanisms of sudden cardiac death in congestive heart failure; 41K

"Silent" heart failure as observed by a French cardiologist; 54K

Spironolactone and altizide in systemic hypertension: ambulatory multicenter study; 24K

Spironolactone and altizide used in combination with enalapril: twenty-four-hour ambulatory recording of blood pressure; 33K

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Symposium: Technetium-99m Myocardial Perfusion Imaging Agents and Their Relation to Thallium-201

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Technical aspects of myocardial planar imaging with technetium-99m sestamibi; 16E

Technical aspects of myocardial SPECT imaging with technetium-99m sestamibi; 23E

Thrombolytic therapy for myocardial infarction: assessment of efficacy by myocardial perfusion imaging with technetium-99m sestamibi; 36E

Use of technetium-99m sestamibi to determine the size of the myocardial area perfused by a coronary artery; 85E

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Symposium: Triggering and Circadian Variation of Onset of Acute Cardiovascular Disease

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Lipid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lipid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lipid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lipid group (43 vs 27 patients in the placebo group, $p=0.056$).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lipid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lipid group and none in the placebo group ($p=0.06$; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lipid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lipid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lipid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lipid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lipid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lipid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lipid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lipid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lipid, may occasionally be associated with myositis. Patients receiving Lipid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lipid therapy should be withdrawn.

Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

CAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain if the lipid levels are consistently abnormal. Before instituting Lipid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and thyroidism that are contributing to the lipid abnormalities.

Continued Therapy—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

Drug Interactions. (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of therapy or after several months. In most subjects who have had an unsatisfactory response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of serum CK levels will prevent the occurrence of severe myopathy and kidney damage.

Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LIPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

Oogenesis, Mutagenesis, Impairment of Fertility—Long-term studies conducted in rats and mice at one and ten times the human dose. The incidence of liver nodules and liver carcinomas was significantly increased in high dose rats. The incidence of liver carcinomas increased also in low dose males, but was not statistically significant ($p=0.1$). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver tumors. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lipid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lipid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lipid is tumorigenic in male and female rats, the use of Lipid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lipid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lipid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lipid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lipid is discontinued. Therefore periodic liver function studies are recommended and Lipid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lipid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lipid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lipid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lipid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lipid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lipid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lipid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdose, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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240 TOTAL
<35 HDL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,¹ and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.²

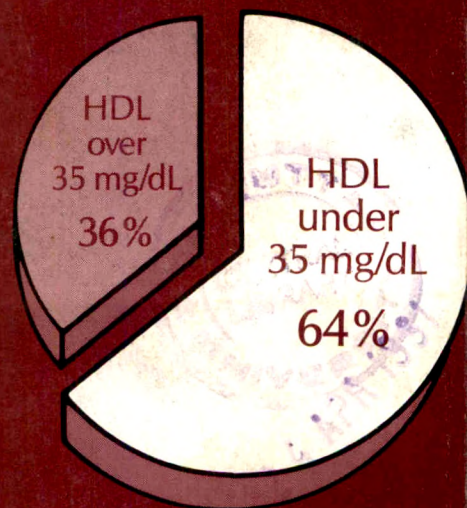
HEART ATTACK PATIENTS
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LOPID raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS)³

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).³



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BID

RAISES HDL...DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. 2. Assmann G, Schulte H. PROCAM-Trial: Prospective Cardiovascular Münster Trial. Zürich: Panscientia Verlag; 1986:8-9. 3. Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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